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EDITORIAL

VACCINATION AGAINST TUBERCULOSIS

The BCG (bacille Calmette-Guérin) vaccination against tuberculosis, first used in France more than 30 years ago, has been the subject of much controversy. It has, however, come to be accepted in many countries as an effective method of preventing progressive tuberculosis. The vaccine has been used in various ways, for instance in the newborn and in Mantoux-negative persons exposed to contact with infectious cases of tuberculosis; but no adequate statistical study has been made of the contribution it might make to the further control of tuberculosis in western communities where without its aid the substantial reduction in the prevalence of the disease has taken place which has been a feature of recent decades. Accordingly the Medical Research Council, in 1949, appointed a special committee to plan and direct an investigation in England. This committee has now presented its first report[1]—a progress report—which proves to be a most important document. The report is published in the *British Medical Journal*, and a summary of the report will be found in our present issue (page 388).

A live bacillus prepared from the microbacterium of vole tuberculosis has been used for vaccination against tuberculosis, though on a smaller scale than BCG, and the MRC investigation was planned to assess the value of both of these vaccines.

The investigation was designed to afford a comparison of the incidence of tuberculosis over a period of years in adolescents, divided according to their reaction to the tuberculin test and, in negative reactors, according as they were vaccinated with BCG, vaccinated with vole-bacilli, or unvaccinated.

Between September 1950 and December 1952 about 56,000 volunteers had entered the research—boys and girls nearly all aged between 14½ and 15 and all in their final year at schools in the north of London, at Birmingham and at Manchester. Every entrant had first been

VAN DIE REDAKSIE

INENTING TEEN TUBERKULOSE

Die BCG-entstof (*bacille Calmette-Guérin*) teen tering, wat meer as 30 jaar gelede al vir die eerste maal in Frankryk gebruik is, het baie opspraak verwek. Dit is egter in die loop van jare in baie lande erken as 'n doeltreffende metode om toenemende tuberkulose te voorkom. Die entstof is al op verskillende maniere gebruik, bv. by pasgebore babas en by Mantoux-negatiewe mense wat blootgestel was aan aansteeklike gevalle van tering. Dusver was daar egter nog nie genoeg statistiese navorsing op die bydrae wat dit kan maak tot die verdere beheer van tuberkulose in die westerse lande nie, waar die belangrike afname in die voorkomssyfer van tering—sonder die hulp van hierdie entstof—'n kenmerk van die laaste jare was. Die mediese navorsingraad het dientengevolge in 1949 'n spesiale komitee ingestel om 'n ondersoek in Engeland te beplan en te beheer. Hierdie komitee het so pas sy eerste verslag[1] voorgelê—'n vorderingsverslag—wat 'n baie belangrike dokument blyk te wees. Die verslag het in die *British Medical Journal* verskyn, en op bladsy 388 in hierdie uitgawe van die *Tydskrif* is 'n opsomming daarvan.

'n Lewende basil, voorberei uit die mikrobakterie van tering by die woelmuis (*Microtus agrestis*) word ook as entstof teen tering gebruik, hoewel op kleiner skaal as BCG, en die navorsingraad se ondersoek was ingestel om die waarde van albei vaksines te bepaal.

Die ondersoek was só beplan dat 'n vergelyking getref kon word insake die voorkoms oor 'n aantal jare van tuberkulose by puberteitsjariges. Die proefpersone was verdeel volgens hulle reaksie op die tuberkulientoets, en dié wat negatief gereageer het, is weer verdeel in groepe wat met BCG, met muisbasil, of glad nie geënt is nie.

Tussen September 1950 en Desember 1952 het ongeveer 56,000 vrywilligers hulle vir navorsing aangebied—almal seuns en meisies tussen 14½ en 15 jaar oud, en almal in hul laaste jaar op skool in noord-Londen, Birmingham en Manchester. Van elke kind is eers 'n roentgenbeeld opgeneem, en dié wat teringlyers geblyk het, of wat kort tevore tuis met 'n teringlyer in aanraking was, is uitgesluit uit die ondersoek. (Onder dié wat as toetreders geslaag het, was daar 'n paar wat

X-rayed and any found to be suffering from tuberculosis, or to have been in recent contact with a case at home had been excluded from the investigation. (A few of those who had been passed as entrants were afterwards excluded because they developed tuberculosis which was adjudged to have started before entry.)

At the initial examination each entrant was also given an intracutaneous tuberculin test with 3 TU (tuberculin units), and those who reacted negatively were then tested with 100 TU. Those negative to both strengths were divided into 3 'random' groups, of which one group was at once vaccinated with BCG and one with vole-bacillus, and the third group was left unvaccinated. The positive reactors were divided into 2 groups, viz. those positive to 3 TU and those negative to 3 TU and positive to 100 TU. Thus the 56,000 entrants were divided for purposes of comparison into 5 groups, every member of which from then on has been subjected to a carefully designed and rigorous follow-up, which is still continuing.

Besides the initial examination, many of the participants recieved a second examination (including tuberculin tests and chest X-ray) while still at school, and after leaving school they have all been followed up by means of a cycle of enquiry and examination lasting 14 months and consisting of a postal enquiry, a home visit by a health visitor, and an examination which again included a chest radiograph and tuberculin tests. As a result, contact was made during the cycle with 94% of the participants, and has since been made with many of the remaining 6%. Besides these sources, information was also obtained from notification lists of medical officers of health and from the chest clinics. After the completion of the first cycle a second 14-months cycle of enquiry was put in operation, and so on.

Of the participants who were vaccinated with BCG, 99·6% became tuberculin-positive; of those vaccinated with vole-bacillus 94·4% (the vole-bacillus vaccine used for the earlier participants was below standard strength; of the 1,900 vaccinated with the later batch all became positive).

All definite and suspected cases of tuberculosis that were discovered were examined by an independent assessor, who was kept unaware of the results of the tuberculin tests and whether vaccination had been performed.

A total of 165 definite cases of tuberculosis began within 2½ years after entry to the trial. Of these 63% were of pulmonary tuberculosis and 22% of pleural effusion without evidence of pulmonary tuberculosis; 68% were severe enough for the patients to be taken off work for at least 3 months. There was no death from tuberculosis in any participant during the 2½ years.

The annual incidence of tuberculosis (over the 2½ years) in the tuberculin-negative unvaccinated group was 1·94 per 1,000, in the BCG-vaccinated group 0·37 per 1,000, and in the vole-bacillus-vaccinated group 0·44 per 1,000.

According to the results of the test, if *none* of the tuberculin-negative entrants had been vaccinated 165 cases of tuberculosis would have been expected among them within 2½ years of entry; if all of them had received later weer uitgesluit is omdat hulle tering, wat na vermoede al vóór inskrywing begin het, ontwikkel het.)

By die eerste ondersoek is 'n tuberkulien-veltoets met 3 TU (teringeenhede) op elke inskrywer gedoen, en dié wat negatief gereageer het, is vervolgens met 100 eenhede getoets. Dié wat op albei konsentrasies negatief gereageer het, is toe weer in 3 ,toevallige' groepe verdeel, waarvan een dadelik met BCG, en een groep met die muisbasil geënt is. Die derde groep is nie geënt nie. Die positief-reagerendes is weer in 2 groepe verdeel, nl. positief op 3 eenhede en positief op 100 eenhede. Dus is die 56,000 medewerkers vir vergelykingsdoeleindes in 5 groepe verdeel, en elke lid is van toe af onderwerp aan 'n noukeurig beplande, streng opvolging wat nog aan die gang is.

Benewens die eerste ondersoek, is baie van die kinders vir die tweede maal—weer met inbegrip van tuberkulientoetse en X-straalbeelde van die borskas—ondersoek terwyl hul nog op skool was. Nadat hulle die skool verlaat het, is almal opgevolg deur middel van 'n kringloop van navraag en ondersoek wat oor 14 maande gestrek het en wat bestaan het uit navraag deur die pos, tuisbesoek deur 'n gesondheidsamptenaar, en 'n ondersoek wat wéér straalondersoek en tuberkulientoetse ingesluit het. As gevolg van hierdie metodes het die navorsers gedurende die kringloop met 94 persent van die deelnemers in aanraking gekom, en sedertdien is die meeste van die oorblywende 6 persent ook opgespoor. Afgesien van hierdie bronne, is inligting ook geput uit die kennisgewinglyste van mediese gesondheidsbeamptes en borsklinieke. Na afloop van die eerste kringloop is 'n tweede navraagprogram van 14 maande ingestel, en so voort.

Van die deelnemers wat met BCG geënt is, het 99·6 persent tuberkulien-positief geword, en van dié wat met die muisbasil geënt is, 94·4 persent. (Die muisbasil-entstof waarmee die eerste klomp deelnemers geënt was, was onder die normale sterkte; die 1,900 wat met 'n latere voorbereiding geënt is, het almal positief geword.)

Alle uitgesproke en verdagte gevalle van tering wat ontdek is, is deur 'n onafhanklike geneesheer ondersoek wat nie ingelig is oor die uitslag van die tuberkulientoetse en wat nie geweet het of die pasiënte geënt was of nie.

'n Totaal van 165 uitgesproke gevalle van tuberkulose het binne 2½ jaar na toetrede tot die proefneming begin. Uit hierdie totaal was daar 63 persent gevalle van longtering, en 22 persent gevalle met borsvlies-uitvloeisel sonder tekens van longtering; 68 persent was so ernstig siek dat hulle ten minste 3 maande lank moes ophou werk. Gedurende die 2½ jaar het geeneen van die deelnemers aan tuberkulose gesterf nie.

Die jaarlikse voorkomssyfer van tuberkulose (oor die 2½ jaar) in die nie-geënte tuberkulien-negatiewe groep was 1·94 op 1,000; in die BCG-groep was dit 0·37 op 1,000; en in die groep wat met die muisbasil-entstof geënt was, was dit 0·44 op 1,000.

Bereken op die uitslag van die proefneming, kon dit verwag word dat 165 gevalle van tering binne die 2½ jaar na toetrede sou voorkom onder die tuberkulien-negatiewe groep, as *geeneen* van hulle geënt was nie. As almal van hulle met BCG geënt was, kon 30 gevalle verwag word—dit beteken 'n afname van 82 persent in die verwagte voorkomssyfer van tuberkulose in die tuber-

BCG vaccine 30 cases would have been expected—a reduction of 82% in the expected incidence of tuberculosis in the tuberculin-negative group. This convincing result may be taken as a fair expression of the protection afforded during the first 2½ years to the BCG-vaccinated adolescents in this experiment. The results with vole-bacillus vaccine are equally convincing. Later reports on the experiment must be awaited for an answer to the question how long the protection will endure in the vaccinated subjects; incomplete follow-up results extending to 4 years which are recorded in this first report disclose no falling off.

This figure of 82% applies, as stated, to the tuberculin-negative section, who constituted 60% of the test population of adolescents. The remainder (the tuberculin-positive) could not have the benefit of vaccination. Including them so that the whole of the test population is is under consideration, if *none* had been vaccinated 246 cases of tuberculosis would have been expected in the 2½ years; if *all the negative reactors* had received BCG vaccination 111 cases would have been expected—a reduction of 55% in the incidence of tuberculosis in the whole test-population.

However, 134 cases of previously unsuspected definite tuberculosis which were present on entry were excluded from the trial, nearly all as the result of the initial radiographic examination. In the absence of this X-ray, many of these cases would have been thought to arise after entry, and the apparent reduction in the total incidence of tuberculosis would have been only of the order of 35%.

These figures constitute a strong case in England, and other countries in like case, for proceeding with the vaccination of school children against tuberculosis. The high proportion (40%) of positive reactors at the age of 14 or 15 in this experiment suggests that the vaccination should be undertaken at a younger age; however, more data is needed before the optimum age can be determined. The *British Medical Journal*[2] says: 'Not enough is known to allow the prescription of an optimum age for vaccination, and if there is indeed such an age it may well vary with changing circumstances. The best compromise might be to offer vaccination to school-children as a routine at the age of about 12....and to make vaccination against tuberculosis conveniently available at any age to children whose parents request it.'

The tuberculosis situation in the White population of South Africa is much the same as in the people of Britain. It is known that the Union Government has been seriously considering a scheme of anti-tuberculosis vaccination. The results to date, therefore, of this English experiment should go far in deciding the issue here. There is perhaps an even stronger case for the application of a vaccination scheme to the Native, Coloured and Indian population, who suffer from a greater prevalence of tuberculosis and mostly live in conditions which favour a high incidence of the disease. This view is supported by the results obtained in experimental work in North American Indians,[3, 4, 5] who suffer from a high prevalence of tuberculosis.

In conclusion reference should be made to the significant results obtained by the follow-up of the 40% of participants in the MRC investigation who gave a kulien-negatiewe groep. Hierdie oortuigende uitslag kan beskou word as 'n redelike bewys van die beskerming wat die BCG-entstof gedurende die eerste 2½ jaar van die proefneming aan die kinders verleen het. Die resultate met die muisbasil-entstof is ewe oortuigend. Latere verslae oor die proefneming sal 'n antwoord lewer op die vraag van hoe lank die beskerming by geënte persone sal duur; die tot nog toe onvolledige opvolgingresultate van 4 jaar, wat in hierdie eerste verslag opgeteken is, dui aan dat daar nog geen afname in onvatbaarheid is nie.

Soos aangestip, het die syfer van 82 persent betrekking op die tuberkulien-negatiewe groep, wat 60 persent van al die deelnemers in die proefneming uitgemaak het. Aan die res (die tuberkulien-positiewes) kon die voordele van inenting nie verstrek word nie. As ons hulle ook insluit om ons berekening oor die hele proefpopulasie uit te brei, kon 246 teringgevalle in die 2½ jaar verwag word as geeneen van hulle geënt was nie; gestel *al die negatiewes* het die BCG-enting gekry, kon daar 111 gevalle verwag word—'n afname van 55 persent in die voorkomssyfer van tering in die hele proefneminggroep.

Daar was egter 134 gevalle van voorheen onvermoede maar definitiewe tering aanvanklik teenwoordig, wat toe uit die proefneming uitgesluit is, meestal as gevolg van die eerste radiografiese ondersoek. Sonder hierdie straalondersoek sou die navorsers gedink het dat baie van hierdie gevalle eers na toetrede ontwikkel het, en dan sou die klaarblyklike afname in die totale voorkomssyfer van tuberkulose maar omstreeks 35 persent gewees het.

In Engeland, asook in ander vergelykbare lande, pleit hierdie syfers oortuigend ten gunste daarvan dat die inenting van skoolkinders teen tering voortgesit word. Die groot proporsie (40 persent) in hierdie proefneming van positief-reagerendes op 14 of 15 jarige ouderdom, suggereer dat die inenting miskien op 'n jonger leeftyd gemaak moet word; meer gegewens is egter nodig om die beste ouderdom te bepaal. Die *British Medical Journal*[2] doen die volgende verklaring: ‚Not enough is known to allow the prescription of an optimum age for vaccination, and if there is indeed such an age it may well vary with changing circumstances. The best compromise might be to offer vaccination to school-children as a routine at the age of about 12....and to make vaccination against tuberculosis conveniently available at any age to children whose parents request it.'

In Suid-Afrika is die tering posisie by Blankes min of meer dieselfde as in Brittanje. Dit is bekend dat 'n skema van inenting teen tering die ernstige aandag van die Unie-regering geniet. Die huidige resultate van hierdie Engelse proefneming kan heel moontlik baie help om die deurslag te gee. Miskien is die toepassing van 'n inentingskema meer dringend by die Naturelle-, Kleurling- en Indiër-bevolking waar die voorkomssyfer van tering soveel groter is en wat gewoonlik onder omstandighede lewe wat 'n groot voorkomssyfer begunstig. Hierdie mening word ondersteun deur die resultate van proefnemings by Noord-Amerikaanse Indiane[3, 4, 5] by wie die voorkomssyfer van tering baie hoog is.

Ten slotte moet daar verwys word na die betekenisvolle opvolgingsresultate van die 40 persent deelnemers aan die Britse navorsingraad se ondersoek wat positief gereageer het op die eerste tuberkulientoets. Dit is

positive reaction in the initial tuberculin test. It was found that in those with a positive reaction to 3 TU the annual incidence of tuberculosis (in 2½ years) was 1·75 per 1,000, and in those negative to 3 TU and positive to 100 TU 0·74 per 1,000. The incidence was particularly high amongst those with *strong* reactions to 3 TU. In those with 15 mm. induration or more the annual rate was 2·93 per 1,000 and in those with 5-14 mm. induration 0·78 per 1,000. These figures are to be compared with the annual incidence of 1·94 per 1,000 in the tuberculin-negative unvaccinated group. They point to the desirability of keeping persons with *strong* tuberculin reactions under close observation.

A further interesting feature of the follow-up was that in the unvaccinated negative reactors the tuberculosis incidence rate was low in the first year and higher in the second year, by which time it reached the same levels as those with high tuberculin sensitivity. This may possibly be correlated with the fact that after the adolescents leave school they begin, in employment, to run a greater risk of infection. On the other hand, in the positive reactors on the whole the incidence of tuberculosis was fairly even over the first 3 years.

1. *Tuberculosis Vaccines Clinical Trials Committee* (1956): Brit. Med. J., **1**, 414.
2. *Editorial* (1956): *Ibid.*, **1**, 444.
3. Aronson, J. D. (1948): Amer. Rev. Tuberc., **58**, 255.
4. Aronson, J. D. and Aronson, D. F. (1952): J. Amer. Med. Assoc., **149**, 334.
5. Stern, S. C. and Aronson, J. D. (1953): Amer. Rev. Tuberc., **68**, 695.

bevind dat die jaarlikse teringvoorkomssyfer in die 2½ jaar 1·75 op 1,000 was by dié wat positief reageer het op 3 eenhede, en 0·74 op 1,000 by dié wat negatief was op 3 eenhede en positief op 100 eenhede. Die voorkomssyfer was veral groot by dié wat *sterk* gereageer het op 3 eenhede. By die proefpersone met 'n verharding van 15 of meer mm. was die jaarlikse voorkoms 2·93 op 1,000, en by dié met 5-14 mm. verharding was dit 0·78 op 1,000. Hierdie syfers moet vergelyk word met die jaarlikse voorkomssyfer van 1·94 op 1,000 by die tuberkulien-negatiewe, nie-geënte groep. Hulle dui op die wenslikheid daarvan om mense met sterk reaksies op tuberkulien noukeurig dop te hou.

Nog 'n interessante kenmerk van die opvolging was dat die voorkomssyfer van tuberkulose by die nie-geënte, negatief-reagerendes laag was in die eerste jaar, en hoër in die tweede jaar, toe dit dié van die hoogs sensitiewe tuberkulien-reagerendes ingehaal het. Moontlik kan dit in verband gebring word met die feit dat die jongmense groter gevaar van aansteking loop as hulle eers die skool verlaat en begin werk. Aan die ander kant was die voorkomssyfer by die positief-reagerendes oor die algemeen taamlik eweredig oor die eerste 3 jaar.

1. *Tuberculosis Vaccines Clinical Trials Committee* (1956): Brit. Med. J. **1**, 414.
2. *Editorial* (1956): Ibid., **1**, 444.
3. Aronson, J. D. (1948): Amer. Rev. Tuberc., **58**, 255.
4. Aronson, J. D., en Aronson, D. F. (1952): J. Amer. Med. Assoc., **149**, 334.
5. Stern, S. C. en Aronson, J. D. (1953): Amer. Rev. Tuberc., **68**, 695.

PORPHYRIA

Porphyria is a disease of special interest because of its familial incidence and its habit of remaining latent until on specific provocation which can be avoided if the danger is realized, it breaks out into its serious, and often fatal, acute phase. The disease is not uncommon in South Africa, in both Europeans and non-Europeans. In Europeans nearly all cases are of old Afrikaner stock, and it has been shown to be a non-sex-linked Mendelian dominant.

Dr. Geoffrey Dean, whose article is published in this issue (page 377), has traced the genealogies of 32 porphyric families, in which a total of 324 members (168 male and 156 female) are known to have shown clinical manifestations of porphyria. One of these groups, which was intensively investigated (Dean and Barnes), descends from an ancestor who was born in 1814 and had had 478 descendants, 434 of whom were still alive. With these, contact was established and specimens of urine were obtained from them. One porphyric parent in the group has 125 descendants (excluding those under 18 years old), of whom 60 are porphyrics, extending over 5 generations; and the history of the disease in this branch conforms entirely with the requirements of a non-sex-linked Mendelian dominant.

In the latent stage of porphyria the symptoms may be mild or absent. It usually causes no symptoms during childhood. The commonest manifestation is abnormal sensitivity of the exposed skin, which blisters and abrades easily and is sometimes more pigmented than usual. This skin condition is commoner in men; in women pre-auricular hypertrichosis may occur. Most male porphyrics remain well throughout life, but many of the women complain of abdominal discomfort, which sometimes leads to a laparotomy, with its special dangers for a porphyric. During pregnancy symptoms are often more pronounced, and a history may be given that previous pregnancies were terminated because of pains, vomiting and hysteria. Often a family group is found to be porphyric only when one of its members has an acute attack.

The diagnosis of porphyria is determined by analysis of the urine and faeces. In the latent stage the urine is normal in appearance and the increase in porphyrin may be so slight as not to be easily detected; it may even be absent. In the acute stage the diagnosis may be suggested by a dark urine of reddish-brown colour. In both stages the urine should also be tested for porphobilinogen which, however, is seldom present in the quiescent stage. More precise information can be obtained by a quantitative analysis of faecal porphyrin. For analysis, 4 oz. of urine, with a few drops of chloroform added, and a sputum-jar half full of faeces, should be sent to a biologist skilled in porphyrin analysis.

An acute attack is readily provoked by drugs, chemicals or alcohol, and, in Dean's experience, is always precipitated in this way. A wide range of drugs has this action,

particularly sedatives such as barbiturates. Thiopentone as an anaesthetic is extremely dangerous. If an operation is necessary, gas, oxygen and ether may safely be given. Penicillin is not harmful, but sulphonamides are dangerous.

In the acute attack of porphyria the behaviour is very emotional, the patient complains of severe pain all over the body and especially in the abdomen, nutrition is impaired, usually with marked loss of weight, and vomiting and constipation may occur. Weakness of the limbs may follow, which may at first be attributed to hysteria but is in fact caused by a lower-motor-neurone type of paralysis; the reflexes disappear, pupils are dilated, pulse is rapid, and blood pressure may be raised. There is evidence of impared liver-function and usually leucocytosis. Sometimes epileptic convulsions occur. Acute porphyria is much commoner in women than in men.

We cannot do better than quote in conclusion the last paragraph of Dr. Dean's article:

'Once a case of porphyria has been diagnosed it is the doctor's responsibility to investigate the family history fully....Enquiry must be made to discover which side of the family is affected....The urine and faeces of the relatives on the affected side should be examined for porphyrins. It must not be forgotten that the syndrome will present in different ways in different members of the family. Some may have complained of symptoms the cause of which will not have been known, and the doctor will be able to make the correct diagnosis in patients who have long been regarded as neurotic. All affected members of the group should be interviewed, and they should be given a letter stating the evidence on which the diagnosis has been made and mentioning the danger of barbiturates and other drugs in this condition; this letter they should show to any doctor they may consult in future.'

PORPHYRIA, A FAMILIAL DISEASE: ITS DIAGNOSIS AND TREATMENT

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Porphyria, a disorder involving profound disturbances in the metabolism of pyrrole pigments, is common in South Africa and occurs in both Europeans and non-Europeans.[1,5] In Europeans it is a familial disorder inherited as a non-sex-linked Mendelian dominant characteristic, and causes cutaneous, psychological and neurological symptoms. In South Africa nearly all European cases are of old Afrikaner stock and a future paper will show that these cases are descendants of one forbear who came to this country nearly 300 years ago. A very rare form of 'congenital' porphyria, with marked skin sensitivity, pink staining of teeth and bone, anaemia and enlarged spleen is also occasionally seen. This form is inherited as a Mendelian recessive characteristic.[6,8]

Familial porphyria usually causes no symptoms in childhood; although on average one in two children of a porphyric parent inherit the disorder, it is difficult to decide which have done so before adult life is reached. Even in adults the symptoms in the latent stage may be very mild or absent; usually, however, there is a slightly increased sensitivity of the exposed skin, which blisters and abrades easily, and a few scars may be present on the back of the hands (Fig. 1). The skin sensitivity is generally more pronounced in men, although many woman who inherit the disorder do know that their skin is slightly more sensitive than average and may remember a time when it blistered easily. A useful test is to scrape the skin on the back of the hand 4 or 5 times with a finger nail; in porphyria the superficial layer often abrades. The skin is sometimes more pigmented than usual and the women may show pre-auricular hypertrichosis. Enquiry may reveal that other close relatives also suffer from a sensitive skin, but repeated and careful questioning may be necessary. Although most male porphyrics remain well throughout life, many of the women complain of abdominal discomfort and they are likely to be given barbiturate sedatives, which then aggravate the condition. If abdominal pains are acute, appendicitis, intestinal obstruction or some other abdominal emergency is often diagnosed and the abdomen may be opened after administration of a thiopentone anaesthetic. This anaesthetic nearly always precipitates an attack of acute porphyria. During pregnancy symptoms are usually

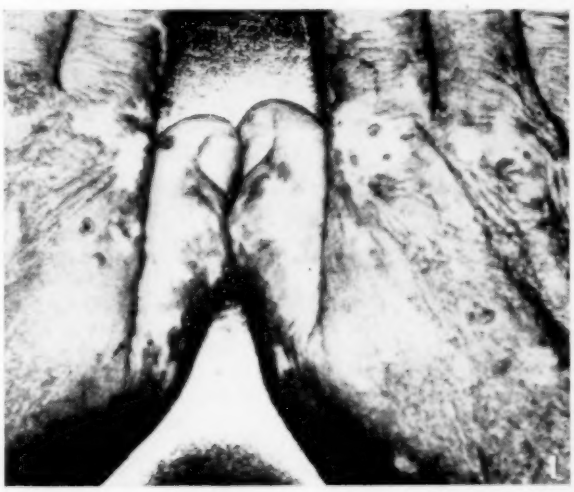

Fig. 1. Skin sensitivity in porphyria. These hands show blisters, sores and healed de-pigmented scars. The lesions are not usually so marked even in male porphyrics.

more pronounced and there may be a history that previous pregnancies were terminated because of pains, vomiting and hysteria. Sub-acute porphyria may be mistaken for Addison's disease, but examination of the urine and faeces will settle the diagnosis. In this country porphyria is common and Addison's disease is rare. Hysteria, mental disorder and hyperthyroidism may also be considered in the differential diagnosis.

In many cases a family group is first found to be porphyric when one of its members has an acute attack. In my experience acute attacks are always precipitated by drugs, chemicals or alcohol. Attacks of acute porphyria occur much more frequently in women, although both sexes inherit the disorder equally and skin sensitivity is usually more marked in men. The reason for the predominance of acute attacks in women is not fully understood; there may be endocrine factors, and perhaps women are more liable to take sedatives and to be operated upon for abdominal pain. Acute attacks are commoner in pregnancy—a time when sedatives are often prescribed. Porphyria is one of the few conditions where the doctor may be responsible for the patient's acute illness and perhaps death.

In an acute attack of porphyria the behaviour is very emotional. The patient complains of severe pain all over the body but particularly in the abdomen. Nutrition is often difficult to maintain, there may be vomiting and constipation, and there is usually a marked loss of weight. Unless the symptoms subside she will soon complain of weakness in the limbs, which at first may be regarded as hysteria; then in a few days it will be realized that a lower-motor-neurone type of paralysis has developed. The reflexes disappear, the pupils are dilated, the heart rate is rapid and the blood pressure may be raised. If the patient does not die the peripheral neuritis may persist for many months. During an acute attack there is evidence of impaired liver-function and usually a leucocytosis. The cerebrospinal fluid is normal. The electrocardiograph shows a tachycardia but no characteristic change. In some cases epileptic convulsions occur. The urine is reddish-brown in colour and darkens on standing; a great excess of porphyrin and porphobilinogen will be present.

THE INHERITANCE OF PORPHYRIA

In order to study the inheritance of porphyria the author has now traced the genealogies of 32 porphyric family groups, all of old burgher stock. A total of 324 members (168 male and 156 female) had clinical manifestations of porphyria. One of these family groups, which is typical of the others, was intensively investigated (Dean and Barnes[4]); see Fig. 1. The forbear of this group, born in 1814, had had 478 descendants, 434 of whom were still alive. Members of this family were traced to Germany, France, England, the United States and the Rhodesias. All living members of the family were contacted and after considerable perseverance specimens of urine were obtained from all of them and examined for porphyrin. In many cases a number of specimens of urine were examined and a quantitative analysis made of faecal porphyrin.

According to Mendelian law, if a dominant characteristic is present in one partner only, half the descendants should inherit the dominant characteristic. There are 60 porphyrics among the 125 descendants of a porphyric parent in this group, excluding those under the age of 18 years. In all cases only one parent is a porphyric. Five of the 10 children in the 2nd generation are porphyrics. In the 3rd generation there are 16 porphyrics among the 37 children with a porphyric parent. In the 4th generation there are 32 porphyrics among the 59 children with a porphyric parent. In the 5th generation there are 7 porphyrics among the 19 descendants with a porphyric parent, all young but over the age of 18 years. In this family 48% of the adults with one porphyric parent inherited porphyria; 24 out of the 41 male descendants with a porphyric parent and 36 out of 84 female descendants. These figures conform with the theoretical requirements of a non-sex-linked Mendelian dominant type of inheritance.

Only 4 of the 36 women who inherited porphyria had severe skin sensitivity; 14 of the 36 have died, and 8 of the 14 died with typical symptoms of acute porphyria. Of the 25 men, 8 have died, but only 1 from acute porphyria; of the 17 who are alive 16 have scars on their hands from previous sores and the skin of their hands is easily abraded. Most of them are free of symptoms except for the skin sensitivity, and do not take drugs. Acute porphyria is much less common in male porphyrics.

CASE HISTORIES

The following are typical cases of acute porphyria from this family:

III. 6. Male, died aged 46, Johannesburg (1932). Since he was a young man, his wife says, he had had a sensitive skin that blistered easily. He often complained of attacks of abdominal pain and when he was 30 a laparotomy was carried out. His final illness occurred while he was taking barbiturates; he complained bitterly of abdominal pain, frequently vomited and was very constipated. He lost 80 lb. in weight. A barium meal showed some delay in the small bowel and a bromethol anaesthetic was given by rectum so that a laparotomy could be performed; he died before the abdomen was opened. His hospital notes state that his urine was port wine in colour. Of his 5 children 4 are porphyrics.

III. 51. A woman died aged 57, Bloemfontein (1949). She had suffered periodically throughout her adult life from attacks of abdominal pain. Her skin did not blister but was unduly sensitive. During her last illness barbiturates were prescribed for her; her pains increased, she lost 40 lb. in weight and complained of marked weakness in her arms and legs. She was admitted to hospital where her urine was 'port wine in colour'; porphyrin and porphobilinogen was present. She became paralysed and died.

III. 58. Morgenzon, Transvaal (1953). This woman was traced during this investigation. Her urine was negative when tested for porphyrins but her daughter's urine was positive. She was warned that she was a porphyric and that certain drugs were dangerous, particularly sedatives and especially a 'pentothal' anaesthetic. She was asked to show her doctor the warning letter. In spite of these precautions she allowed her doctor to give her a thiopentone anaesthetic and developed an acute attack of porphyria with paralysis. She then produced the warning letter, the diagnosis was confirmed, all drugs were stopped and she slowly recovered over a period of months.

IV. 3. A woman died aged 40, Cape Town (1953). This member of the family was only traced with great difficulty after about 2 years' research. A letter was sent to her warning her that she might be a porphyric and asking for a specimen of urine. Her daughter replied and described how her mother had suffered from a sensitive skin and attacks of abdominal pain for many years; how a few days before the arrival of the letter she had started taking Nembutal

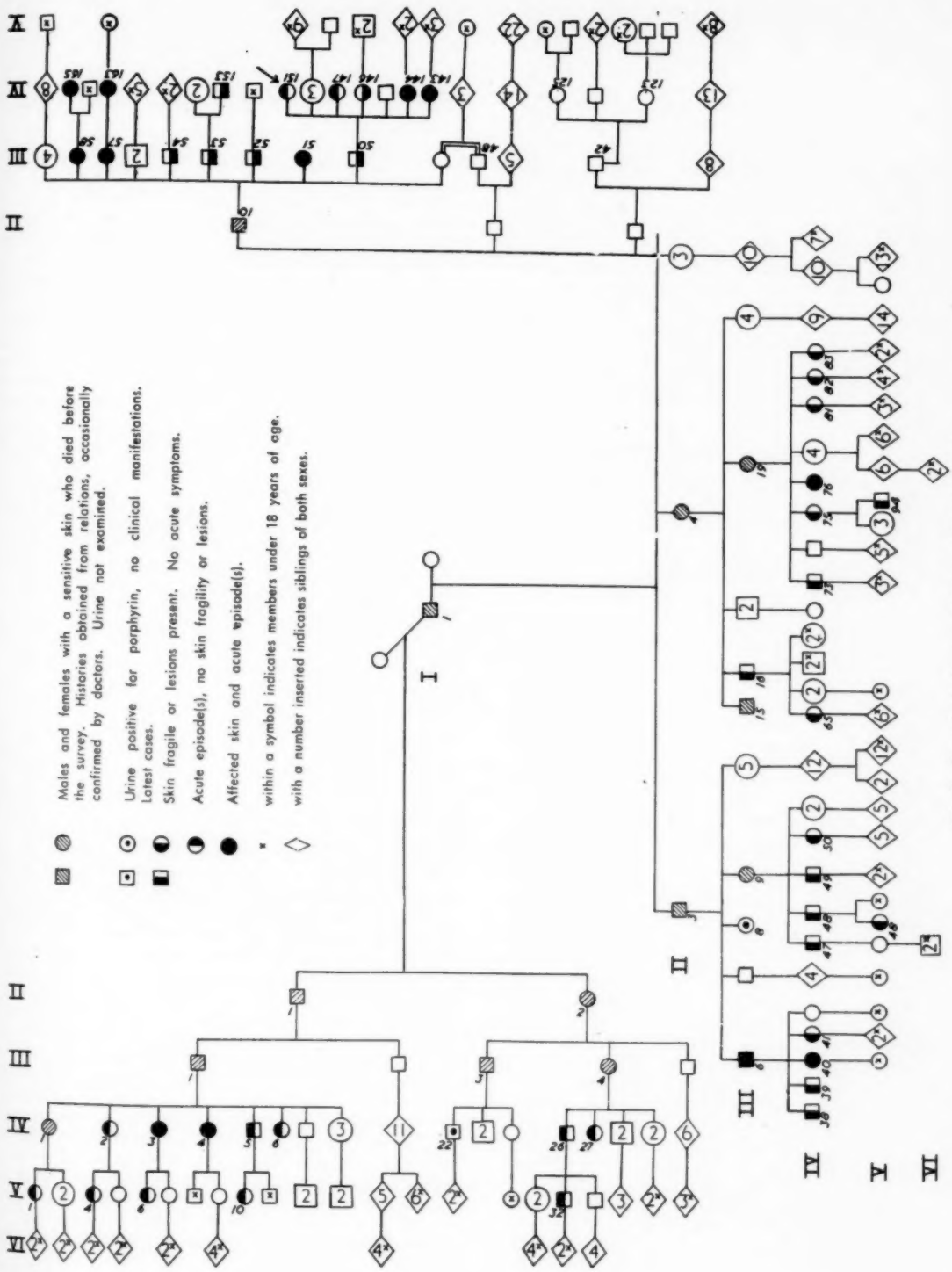

Fig. 2. Genealogical tree. (*British Medical Journal*)

at night. Her pains increased and she became delirious and passed a red urine. The urine contained a great excess of porphyrin and porphobilinogen. She became paralysed and died a few days later. The letter warning her was just too late.

IV. 4. A woman died aged 33, in France (1928). The husband of this woman was last heard of in 1928 at the time of his wife's death. He was eventually traced to his home in France through the assistance of the Cardiff police. He described how his wife had suffered from a sensitive skin and recurrent attacks of abdominal pain. After taking certain drugs at the beginning of her 3rd pregnancy she developed severe abdominal pain, became delirious and passed red urine. Over the course of a few days she became paralysed and died. Death was certified as due to 'blackwater fever'.

IV. 151. A nurse, aged 19, Uitenhage (1951). This case was seen by the author and led to detailed study into this family group. Her skin was slightly sensitive but did not blister. She had always been of a nervous disposition and often complained of pains in her abdomen and limbs. She started taking barbiturate drugs in large doses and her abdominal pains increased, she vomited frequently and was extremely constipated, and she was thought to have an intestinal obstruction. A laparotomy was performed and thiopentone was used to induce anaesthesia. After the operation her symptoms increased and over the course of a few days she became completely paralysed. Her urine was dark amber in colour and the Ehrlich's test for porphobilinogen was strongly positive; although all sedatives were stopped as soon as the diagnosis was made, she died 2 days later.

IV. 163. A woman died aged 24, Durban (1950). For 3 years before her death she complained of attacks of abdominal pain. She was given barbiturates but her symptoms increased, she vomited frequently and was very constipated. She lost a great deal of weight. She was admitted to hospital where it was noted that her urine was 'port wine in colour'. She developed a generalized paralysis and died.

IV. 165. A woman, aged 24. Acute porphyria (1954). She was traced during the investigation of the family and her urine was found to contain porphyrin. The danger of drugs was emphasized. Seven months later, believing herself pregnant, she took certain drugs and developed an attack of acute porphyria. She showed the doctor attending her the warning letter, all sedatives were stopped, and she recovered.

TESTS FOR PORPHYRINS

In the latent stage the urine is normal in appearance. The increase in porphyrin excretion may be so slight that it can only be detected by careful spectroscopic examination of a layer several inches deep; the urine may even be normal. However, the characteristic bands of porphyrin can frequently be detected by those who have experience in spectroscopic examination. Porphobilinogen is seldom present in the quiescent phase. An extract from the faeces will usually show brilliant red fluorescence in ultra-violet light. Normal faeces shows green fluorescence or a slight pink, with a Wood's filter. A fragment of faeces is placed in a small test-tube and dissolved, with the aid of a glass rod, in ½ inch of a mixture consisting of amyl alcohol, glacial acetic acid and ether. More precise information can be obtained by a quantitative analysis of faecal porphyrin[9] and this analysis is essential in doubtful cases. If latent porphyria is suspected, 4 ounces of urine, with a few drops of chloroform added as a preservative, and a sputum jar half full of faeces should be sent to a biochemist specially trained in porphyrin analysis.

In the acute stage the urine may immediately suggest porphyria because of its reddish-brown colour, and it will darken considerably on standing, particularly after the addition of hydrochloric acid. The fresh urine should also be tested for porphobilinogen by the Watson-Schwartz test. Ehrlich's aldehyde saturated with sodium acetate should be added to 5 ml. of urine, and the mixture shaken with chloroform; when porphobilinogen is present a purple colour will remain in the aqueous layer. Urine in acute porphyria will show marked red fluorescence in ultra-violet light, and the presence of porphyrin is confirmed by spectroscopic examination. It should be remembered that blood, beetroot and certain drugs may also cause a red urine.

TREATMENT

When porphyria is diagnosed treatment consists primarily in stopping all drugs that may be aggravating the condition. This includes a wide range of substances, particularly sedatives such as barbiturates. The doctor must advise the patient that there may be some discomfort, but that all will be well as long as drugs and chemicals that aggravate the disorder, including patent medicines and alcohol, are scrupulously avoided. Penicillin may safely be given, but sulphonamides are harmful. The extreme danger of thiopentone anaesthesia must be pointed out to the patient and to the relatives, and to convince them they should be given a few anonymous case-histories to read. If an operation is unavoidable because of serious organic disease, gas, oxygen and ether can safely be given but no barbiturates. If the skin is photosensitive the patient should keep out of the sun as much as possible and wear a hat and keep his sleeves down out of doors. Protective creams, such as 5% tannic acid in vanishing cream, are of some value for the hands. In the very rare 'congenital' disorder splenectomy may lessen the anaemia and porphyrin production.

In the acute stage good nursing, preferably in a private room in a hospital, is the most important single factor in aiding recovery. As there is as yet no specific antidote for porphyria, treatment depends on maintaining the patient's general condition and avoiding harmful drugs. These patients do best if given no sedatives whatever. In my experience it is possible to keep them fairly comfortable during the acute attack with the aid of cortisone and placebos such as vitamin tablets. Kind but firm nursing is essential, and visitors should be discouraged. If there is vomiting the nutrition and electrolyte balance must be carefully watched and maintained by intravenous feeding. Repeated examination of the blood and urine chlorides and the blood potassium may be required. As there is often evidence of liver damage I give these patients a high-protein, high-carbohydrate diet and high fluid-intake. ACTH or cortisone makes them feel better and appears to be of definite value; 25 mg. of cortisone may be given 6-hourly for 2 or 3 days and then half this dose for a similar period. As an aid to general nutrition I give daily 2 ml. of whole-liver extract by injection and a multi-vitamin preparation. Convulsions are best controlled in my experience by 30% ether in oil given over a period of hours by rectal drip. At the same time Epanutin may be given (1½ gr. 6-hourly) by stomach tube. The patient can also be fed through the tube. After ether has been given the rectum should be irrigated with normal saline. In the recovery stage physiotherapy is of great value if paralysis has occurred.

Once a case of porphyria has been diagnosed it is the doctor's responsibility to investigate the family history fully and the best method is to work out a family tree, which may take several months to complete if a number of generations are studied. Enquiry must be made in order to discover which side of the family is affected and which members on the affected side have inherited porphyria. The urine and faeces of the relatives on the affected side should be examined for porphyrins. It must not be forgotten that the syndrome will present in different ways in different members of the family. Some may have complained of symptoms the cause of which will not have been known, and the doctor will be able to make the correct diagnosis in patients who have long been regarded as neurotic. All affected members of the group should be interviewed, and they should be given a letter stating the evidence on which the diagnosis has been made and mentioning the danger of barbiturates and other drugs in this condition; this letter they should show to any doctor they may consult in future.

SUMMARY

Porphyria, a potentially serious familial disorder, is common in South Africa. In Europeans it is inherited as a non-sex-linked Mendelian dominant characteristic. A clinical genealogical study is recorded of 32 porphyric families in which 324 members had clinical manifestations of porphyria.

In the latent stage diagnosis depends on a full personal and family history, with special reference to skin sensitivity in the family, 'nervous breakdowns', abdominal pains, operations, pregnancy, and drugs that have been taken. The diagnosis can usually be confirmed in the quiescent stage by careful examination of the urine and faeces for increased porphyrin excretion. This should be carried out by a biochemist with experience in quantitative porphyrin analysis.

Acute porphyria must be considered in the differential diagnosis of all cases of severe abdominal pain, and the abdomen should not be opened until the urine has been examined. In an acute attack the urine is reddish-brown in colour and excess porphyrin and porphobilinogen will be present.

Prevention of acute attacks is the most important part of treatment. Barbiturate drugs are especially dangerous. If one case of porphyria is diagnosed enquiry will usually reveal several other cases among the relatives, who can then be warned of the inherent danger.

Porphyrics should be given a letter stating the evidence that confirms the diagnosis and mentioning the danger of certain drugs. They should be instructed to show the letter to any doctor they consult in the future.

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THE CARE OF THE PROSTATIC CAVITY*

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The object of this short paper is not to advocate any one method of prostatectomy. I do not intend to revive the controversy of abdominal, perineal or endoscopic prostatectomy, for each of these methods has its advantages and disadvantages; each has its place and its skilled proponents. Generally speaking, there is no best method of removing the prostate gland; individual skill and experience counts for a great deal and each case of obstruction has to be considered on its merits; it is far better to fit the operation to the patient than the patient to the surgeon.

This paper will describe a method that has been used in 120 consecutive cases of prostatectomy and will deal mainly with the prostatic cavity and the methods that were employed to control the bleeding initially and in the post-operative course.

* A paper presented at the South African Medical Congress, Pretoria, October 1955. The figures are reproductions of the slides shown by the author in presenting the paper.

Pre-operative Care. This important subject will not be dealt with except to emphasize that the patient with chronic retention and raised non-protein nitrogen deserves very special care. I should, however, like to mention that it is my impression that the pre-operative use of adrenosem plays a very important part in control of the post-operative ooze. In the very apprehensive type of individual Largactil was given pre-operatively, on the same lines as Evipan isused by general surgeons 'to steal the thyroid'. In most cases pre-operative cystoscopy was performed.

SURGICAL TECHNIQUE

As we are dealing with the care of the prostatic cavity, we shall not elaborate on the intricacies of surgical technique. The method of enucleation and the surgical repair of the cavity are shown in Figs. 1-7.*

The bladder is exposed extraperitoneally through a transverse abdominal incision about a finger's breadth

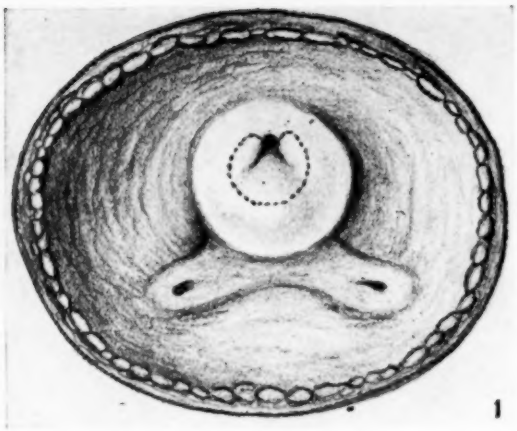

Fig. 1. Typical trilobar enlargement.

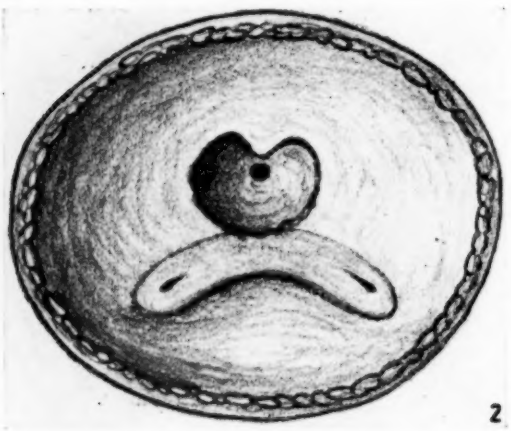

Fig. 2. Cavity after enucleation of adenoma.

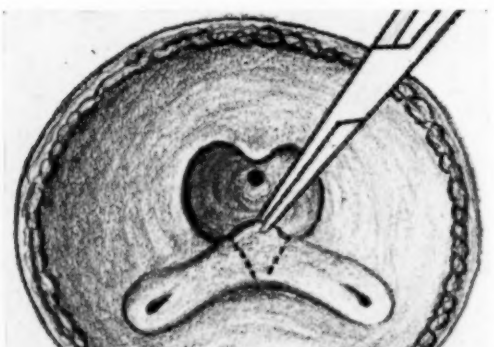

Fig. 3. Posterior wedge resection.

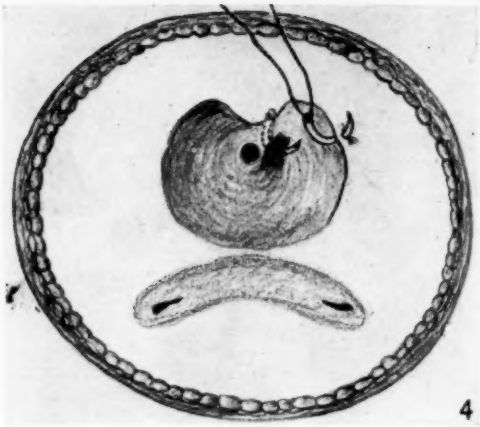

Fig. 4. Suturing of prostatic capsule to mucous membrane.

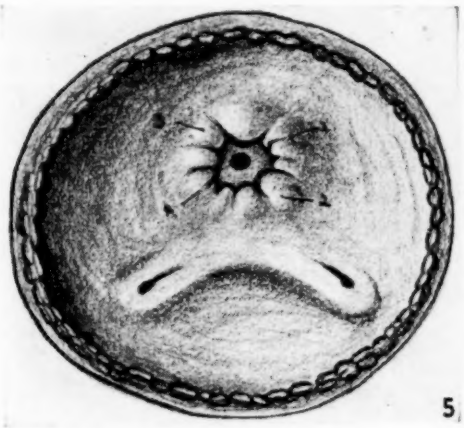

Fig. 5. Invagination of mucous membrane.

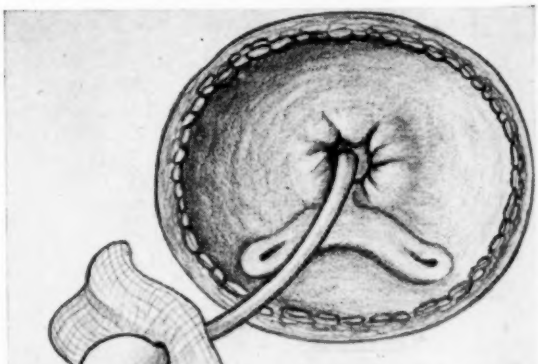

Fig. 6. Inflated Foley's catheter surrounded by Oxycel.

above the symphysis pubis. A Millin's self-retaining retractor is inserted with a posterior blade. Thus adequate visualization is obtained and stones, diverticula or papillomata can easily be seen.

Fig. 1. This is the intravesical view of a typical trilobar enlargement of the prostate. The dotted line shows an incision in the mucous membrane of the bladder overlying the intravesical prostatic protrusion. Note that the incision actually begins in the prostatic urethra at about 11 o'clock and continues circumferentially to 1 o'clock—this is our line of enucleation; the anterior commissure is left intact. A finger is now inserted, a plane of cleavage is found at 11 o'clock, and the gland is enucleated. I would emphasize that the anterior commissure is left intact, for it is very rarely the site of adenomatous involvement. Surely if this, the roof, of the prostatic cavity, is left intact, i.e. with its epithelial lining, the epithelization of the cavity as a whole will be more rapid! The cavity is carefully inspected and all tags of tissue removed by sharp dissection.

Fig. 2. This is the appearance of the prostatic cavity after enucleation of the adenoma. Note that the original incision in the mucous membrane leaves us with a clear-cut margin of mucous membrane surrounding the cavity. A Millin's spreader is inserted into the cavity and all obvious bleeding points are caught and ligated by an under-running suture.

Fig. 3. This shows the performance of a trigonectomy, whereby a liberal wedge is removed from the posterior vesical lip. The advantage of trigonectomy is that the prostatic floor and base of the bladder are brought into one plane. This is important in preventing post-operative bladder-neck contraction.

Fig. 4. This shows a plastic approach to the prostatic cavity whereby a stitch is inserted in the prostatic capsule deep within the cavity and the next bite is through the rim of vesical mucous membrane. When this stitch is tied the mucous membrane is pulled into the prostatic cavity. This stitch is continued around the prostatic cavity from 11 o'clock to 1 o'clock and the result produced shows the mucous membrane well inverted into the prostatic cavity (see Fig. 5). The effect of this stitch is twofold: (1) It produces good haemostasis, and (2) it invaginates the mucus membrane, which will accelerate epithelization.

Fig. 5. At this stage adrenaline in ½% procaine is injected into the prostatic capsule at the 4 points shown. Roughly 5 c.c. is injected at each point. The reasons for this injection are the following: (1) The resulting increase in tissue pressure aids haemostasis; (2) the adrenaline to an extent controls the bleeding; (3) post-operative spasm is relieved; and (4) there is a systemic rise in blood pressure of roughly 15 points—thus any overlooked bleeding point should become obvious.

Fig. 6. A Foley's catheter has been inserted *via* the urethra into the bladder. The bag has been partially inflated and is surrounded by a cuff of Oxycel.

Fig. 7. This shows the inflated bag of the Foley's catheter in the prostatic cavity and between the bag and the actual cavity itself is the Oxycel. It is important to remember that the prostatic capsule contracts

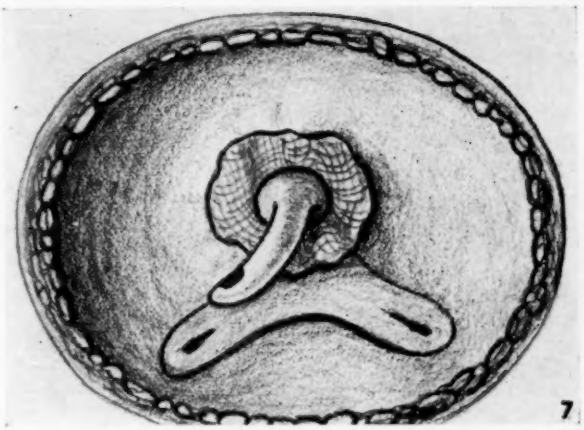

Fig. 7. Inflated Foley's catheter with Oxycel positioned in prostatic cavity.

markedly and therefore the Foley's bag should not be fully distended. Haemostasis at this stage is usually very adequate. Now through a separate stab-wound in the bladder-wall a small Malecot catheter is inserted into the bladder. The end of this is brought out through a stab-wound transversing the skin, subcutaneous tissues and rectus sheath about ½ inch above the original incision. The bladder is now filled with thrombin and closed.

At the conclusion of the operation, besides the small retropubic drain, the suprapubic Malecot emerges through a separate stab-wound. At this stage a bilateral vasectomy is performed.

Many urologists favour the prevention of clot formation in the bladder. Many employ continuous bladder wash-outs, which I am rather against for two reasons, viz. (1) I believe that continuous lavage tends to maintain the ooze from the prostatic cavity and the bladder incision, and (2) it makes it rather difficult to know how much bleeding is taking place because the washout greatly dilutes any blood.

My own method is, after ensuring maximum haemostasis, to employ every known means of ensuring that clotting shall occur, viz. the use of (1) Oxycel, (2) adrenaline with procaine locally into prostatic capsule, (3) Adrenosem systemically, and (4) thrombin locally; and (5) to use no bladder washouts (though an occasional bladder wash-through may be used).

There is no known substance which can be injected locally into the tissues to promote clotting. Adrenaline is primarily a vaso-constrictor and when injected locally will act as such to stop bleeding. On the other hand, adrenaline has a tendency to increase capillary permeability. Adrenaline will not contract capillaries. Thus adrenaline locally will contract the arterioles but has a tendency to increase capillary oozing. Adrenosem will take care of the latter. I have tried Adrenosem locally with inconclusive results.

I feel that we have employed every known method of ensuring haemostasis and maintaining this haemostasis by promoting post-operative clotting and the methods

used are the best available in the light of our present knowledge.

RESULTS

In the 120 consecutive cases there were 5 deaths, which are analysed in Table I. All the deaths were of persons

TABLE I. ANALYSIS OF DEATHS

Case	*Age*	*Condition on Admission*	*Time of Death*	*Cause of Death*
1	82	Gross haematuria	14th Post-operative day	Coronary thrombosis
2	80	Retention	Day of operation	Anaesthetic death
3	70	Retention	5th Post operative day	Unknown cause
4	74	Pneumonia	15th Post-operative day	Pulmonary embolus
5	72	Retention	20th Post-operative day	Carcinoma of liver

over 70 years old, and all were in cases admitted in emergency. In case 5 the patient was passing urine on the 8th post-operative day. He then developed jaundice and died 12 days later, when carcinoma of the liver was found at post-mortem examination.

The *complications* were as follows:

Deaths	4·2%
Haemorrhage	10·0%
Stricture	2·5%
Incontinence	*nil*
Stone in the bladder	1 case
Sinus	*nil*

There were no complications attributable to Oxycel.

Of the 10% of cases with secondary haemorrhage only one was taken back to the theatre to control the bleeding. There were no cases of primary haemorrhage. The post-operative strictures were of slight degree and were adequately treated by intermittent dilatation.

Among the series were 4 patients over the age of 90 years, the oldest being 96.

SUMMARY

1. A simple method of prostatectomy has been described based on:

(i) adequate exposure and clear visualisation,
(ii) clean anatomical enucleation instead of an avulsion,
(iii) haemostasis under direct vision.

Once haemostasis has been secured, the following methods are used to ensure maintenance of the haemostasis and intravesical clotting, viz.:

(*a*) Use of procaine and adrenaline as an intracapsular prostatic injection.

(*b*) Use of a blown-up Foley's catheter surrounded by a cuff of Oxycel.

(*c*) Use of systemic Adrenosem pre-operatively and post-operatively.

(*d*) Use of intravesical thrombin.

(*e*) The avoidance of bladder wash-outs.

I would like to thank Miss P. Trezona for the excellent artistic illustrations; Mr. Cronin of Westdene Products for the liberal supplies of Adrenosem, and Sister van der Merwe of the Far East Rand Hospital, Springs, for her skilled care and constant attention to these prostatectomy cases.

STERILITY AND RETROVERSION*

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In this paper I do not propose to cover all the conditions associated with sterility and retroversion, in many of which the retroversion is incidental and the condition itself the cause of sterility, but to confine myself to those where the retroversion would seem to be, if not the only, at least the main factor. This rules out all the inflammatory conditions, endometriosis, developmental abnormalities, and the like.

We shall therefore only be dealing with those cases where potentially the tubes are patent, the ovaries, at least to begin with, are normal, and the sterility merely mechanical in origin. Such cases may be congenital or acquired.

Let us deal first with an extreme instance of the idiopathic or congenital type, for it is among these that one finds the greatest divergence from what we consider the normal position of the pelvic viscera:

The patient is essentially the thin willowy, aesthetic type that one associates with Vogue and Milady fashion plates, and with general visceroptosis. Her posture is typical; her lumbo-sacral curve is obliterated and she stands with her pelvic floor tilted forward so as to increase the support that it can give to her ptosed viscera, but in spite of this she often complains of continuous backache only relieved by lying on her face.

Pelvic examination shows that her cervix is pointing forwards with the anterior fornix closed, while the posterior fornix is opened up, and this in spite of the fact that her uterus is often acutely retroflexed. The body of the uterus can be readily palpated in the posterior fornix, and frequently prolapsed ovaries as well. The right ovary is usually the first to assume this position, followed later by the left, and if the condition has existed for some time they may both be irregularly enlarged, firm and acutely tender. It is possible at times to diagnose a deep pouch of Douglas or even an enterocele, by making a combined vaginal and rectal examination and at the same time getting the patient to bear down strongly. In this way one can sometimes feel bowel between the examining fingers. These are the cases that respond best

* A paper presented at the South African Medical Congress, Pretoria, October 1955.

to operative treatment and the results are surprisingly good.

On looking into the abdomen with the patient in the Trendelenburg position and with the bladder empty one can see the supravaginal cervix lying in the centre of the pelvis with both ovario-pelvic ligaments disappearing into the depths of the true pelvis on either side of it. At the same time the round ligaments may be seen, usually more or less attenuated, running outwards and forwards to disappear beneath the lateral pelvic peritoneum.

If the sigmoid is lifted out of the pouch of Douglas it will be found to be slung on a long mesentery, and indeed it is often difficult to decide where descending colon ends and sigmoid begins. As we continue this manoeuvre it will be seen that the tube and ovary of this side are dragged out of the true pelvis, attached by a thin transparent membrane to the upper edge of the broad ligament and left tube.

Very little reference seems to have been made to this condition; Curtis refers to its comparative frequency, but he does not seem to attach much significance to it.

After this procedure has been carried out there may still be quite a quantity of sigmoid lying in the pelvis, but it can be pulled up without significantly altering the position of the uterus any further. It seems likely that the constant backache that is so frequently complained of by these patients may be largely due to the drag of the sigmoid on its mesentery and, resulting from its loss of fixity, its inability to drive forward its contents. In consequence, these loops may contain a quantity of hardened faeces.

It can be readily understood, moreover, that when the ovaries have reached a position below the fundus they must be exposed to pressure from these loops; we know they can cause acute dysparunia.

Any further alteration in the position of the uterus must now be made by lifting up the organ itself and, as it comes into view, it often has a rather dusky appearance which gives place quite quickly to a mottled colouring, presumably from patchy contractions, the uterus itself at the same time becoming shorter and broader. This condition soon gives way to its normal colour and texture, and occasionally there seems to be some reduction in its size.

On looking into the pouch of Douglas one sees that the walls of its lowest portion, where the loops of bowel have been lying, are smoothed out and symmetrically rounded, reminding one of the smooth concavity of a bird's nest, with little differentiation of the structures in its walls. The pouch of Douglas is normally deep and may even amount to a true enterocele, as we have already seen.

When the large bowel is allowed to fall back into the true pelvis, the sequence of events is reversed and the retroversion is completed by the left tube and ovary being pulled back into the acutely retroverted position as that portion of the sigmoid which is attached to the upper edge of the broad ligaments and tube falls into its former position.

In the more advanced cases the ovaries have come to lie underneath the fundus, for their ligaments have become sufficiently elongated to allow them to assume this position, the right one usually prolapsing before the left. Under these circumstances they are usually enlarged, with white thickened tunicae, and are full of small follicular cysts varying in size. This thickening of the tunicae is probably a protective mechanism much the same as the protective thickening of the palms of a manual labourer; and this is not to be wondered at, for they have been lying among the coils of prolapsed large bowel, which are frequently full of hard inspissated faeces. The cysts develop in their turn from the inability of the ripening follicle to break through this tunica. It is possible that there may be some alterations in their blood supply, though I would not stress this point. It is certain, however, that the ovaries, after being replaced in their normal fossae, recover, with re-establishment of the usual menstrual cycle, even if nothing is done to them such as removing a thin sliver of their capsule to relieve their tension and allowing developing follicles to dehisce. This often occurs within 3 months of operation, though occasionally it may take much longer.

It is difficult to assess the position of the tubes in these cases, and salpingography does not help very much, for it is not easy to be certain that one has fixed the cervix exactly in its usual position when the radiographs are taken; but usually they appear fairly well out, and one would expect these relative positions in relation to the ovaries to be considerably altered, especially when the latter have developed long ligaments of their own and are lying below the fundus.

We know that the tubes are at times sufficiently kinked to prevent the dye passing out to their extremities, and on two occasions in which I opened the abdomen immediately after salpingography, lipiodol was seen to gush from both fimbriae as the uterus was lifted forward. Professor D. Crichton tells me also of one occasion when lipiodol was seen to flow through the tubes as the full bladder was emptied.

The reaction to alteration of position may account at times for the spill seen into the peritoneal cavity in the picture taken 24 hours later. It may also account for the discrepancy found when both gas and opaque media are used, in that either may be successful where the other has failed.

I feel that it is not stretching the point too much to say that in all cases of retroversion there must be a considerable alteration in the relative position of the tubes and ovaries, even in those of a mild degree, and in those where the ovaries lie below the fundus this must be very marked. That this is the case seems to be born out by the not unfrequent success obtained when the uterus is brought forward by means of a pessary of the Hodge type.

With regard to alterations in the blood supply we have to rely very much on conjecture. Probably the position of the uterine arteries and veins is very little affected as they run inwards from the pelvic wall towards the uterus, but from this point onwards, where they pass alongside the uterus, there must be a considerable deflection backwards and downwards. One can imagine some delay in the venous return, at least where this sudden twist occurs—perhaps sufficient to account for the changes in appearance of the uterus noted earlier on.

When one considers the vessels running in the ovario-

pelvic ligaments, one can imagine that there may be marked alteration in their positions and a certain amount of venous dilated stasis in the ovaries from pressure of the coils of bowel in their vicinity, as well as varying degrees of torsion. This is unlikely to make any difference to the flow of arterial blood, but could easily cause a varying degree of stasis in the veins, according to the degree of fullness of the coils of bowel.

Up till now I have described the condition in its final stage but, as can well be imagined, there must be many intermediate ones before this is reached, especially in those where there is little or no prolapse of the sigmoid and Curtis's adhesion is not present.

RETROVERSION CAUSING STERILITY

Let us examine *seriatim* the reasons why retroversion causes sterility and then show in what manner these can be rectified:

1. First and foremost, the gross alterations in the position of the tube in relation to the ovary. Normally the fimbriated end of the tube lies in close proximity to its corresponding ovary, curving round to hold it as it were in its embrace, and attached to it by an elongated finger. Indeed there is evidence to show that at the time of ovulation the tubal extremity weaves over the ovary. It has been shown by injecting a little opaque medium into it that it moves as though it were searching for the tiny ovum to help it on its incredibly, adventurous and momentous journey. With this close relationship gone the ovum must depend on being picked up fortuitously by some wandering, almost imperceptible, current of capillary fluid which the tube causes to flow towards it by reason of its ciliated lining. This must indeed be a precarious journey, for the life of the ovum is short and it may die, as many must, before it can find its way to the waiting sperm in the tubal lumen.

2. Kinking of the tube preventing the ovum and spermatozoa from meeting.

3. Thickening of the tunicae of the ovary, due to continuous trauma, preventing rupture of the Graafian follicle, which in turn leads to

4. Prevention of the formation of the corpus luteum, with upset of the menstrual rhythm. (This is not invariably so, for in spite of this a corpus luteum is sometimes found at operation.)

5. Severe dyspareunia with consequent infrequency of coitus.

TREATMENT

The following measures may be taken to relieve this condition:

1. *Without Operation*

(*a*) Insertion of a Hodge pessary is sometimes successful. If pregnancy supervenes replace a pessary *post partum* in the hopes that if the uterus is kept in its normal position during involution the ligaments may shorten up in this position.

(*b*) Encourage the patient to sleep on her face, especially round about the ovulation period.

2. *Surgical Measures*

Carry out an operation devised to rectify the malpositions described above:

(*a*) Antevert the uterus so as to bring the ovaries back into their normal fossae, shortening their ligaments if necessary.

(*b*) Draw the cervix backward into its right position, i.e. pointing directly towards the posterior vaginal wall or even backwards.

(*c*) If the ovaries are very sclerosed remove a thin sliver of tissue so as to allow the follicle to rupture with consequent formation of corpus luteum.

The Operation may be done under Pentothal and Flaxedil:

(*a*) Mid-line incision to deep fascia.

(*b*) Expose the fascia in two little pockets ready-made for the purpose about 2 inches above the symphysis pubis.

(*c*) Open peritoneal cavity. Deal with Curtis's adhesion by dividing it and re-suturing in line of bowel and upper edge of broad ligament.

(*d*) Bring together utero-sacrals in the mid-line where they spring from the back of the uterus, with several thread sutures.

(*e*) Shorten ovarian ligaments by Angleworm method.

(*f*) Cover these with peritoneum by means of a fine catgut suture.

(*g*) Treat round ligaments by a modified Gillam's operation, bringing the doubled round ligaments through the inguinal canal on either side and joining them in front of the deep fascia.

Should the pouch of Douglas be very deep the enterocele in its lower portion can be closed by a series of purse-string sutures beginning at the bottom and reaching up as high as thought necessary. This has the disadvantage that there may be cystic formation where this space is not completely obliterated; but this is not likely to occur, and a very small cavity should be left for fluid to reach the base of the new-formed pouch of Douglas.

Caution should be taken to leave sufficient room between the posterior edge of the approximated utero-sacrals and the sigmoid to prevent any bowel from above becoming herniated at this point. This can be easily rectified in the early stages, if such a catastrophe should occur, by making the patient assume the knee-chest position, when the bowel readily falls back out of the pelvis.

UNION DEPARTMENT OF HEALTH BULLETIN

Union Department of Health Bulletin. Report for the 5 days ended 27 March 1956.

Plague. Smallpox. Nil.

Typhus Fever. Cape Province. The result of the laboratory tests of the European case of typhus fever in the Queenstown Municipal area reported in Bulletin No. 12 of 1956, proved negative.

Epidemic diseases in Other Countries

Plague: Nil.

Cholera in Calcutta (India); Chittagong, Dacca (Pakistan).

Smallpox in Kabul, Kandahar (Afghanistan); Moulmein, Rangoon (Burma); Phnom-Penh (Cambodia); Ahmedabad, Bombay, Calcutta, Delhi, Jodhpur, Kanpur, Madras, Mahé, Pondicherry (India); Dacca, Karachi (Pakistan); Nairobi (Kenya).

Typhus Fever in Kabul (Afghanistan).

AN UNUSUAL CASE OF ACUTE INTESTINAL OBSTRUCTION

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The following case has so many unusual features that it is worthy of putting on record.

In July 1955, Daniel Kapp, a boy aged 14, was admitted to the Provincial Hospital, in a very critical state. He had been under medical care for 4 days before admission and he was sent in with a diagnosis of 'obstruction, possibly due to round-worms' and the following history from his medical attendant: 'D.K., European male aged 14 years, had an accident 4 days ago when he fell onto a stick which, according to his parents, pierced the perineum and went 6 inches into his body and had faeces on the tip when withdrawn. On examination there appeared to be only a superficial injury of the perineum and possibly the stick went directly into the rectum, which it may have pierced. It is particularly difficult in this type of patient to coordinate the history with the signs, for it is difficult to know how many inches were added to give a better impression. He complained of severe abdominal pain and passed blood-stained faeces, then became constipated, with abdominal distension and tenderness, vomiting and signs of intestinal obstruction. He also has a round-worm infection, which may be the cause of obstruction. Peritonitis was considered a possible diagnosis, but the temperature was not typical, only going up to 99·4° F. It was only after 4 days that the pain became so severe that it was necessary to prescribe Pethedine. On the following morning there was a definite change in the boy's condition and a diagnosis of obstruction was made.'

On admission the boy was extremely ill, the abdomen was greatly distended and tender, the temperature was sub-normal, the pulse was rapid and feeble, and he was vomiting copiously; the eyes and cheeks were sunken, the face was flushed, and the tongue was dry and covered with foul fur; in fact he looked typical of acute generalized peritonitis in the last stages. A tentative diagnosis was made of acute generalized peritonitis, secondary to traumatic rupture of the rectum by a stick, and it was decided that in spite of his condition an operation should be done, though the chances of survival appeared to be slender.

After preliminary preparation, including intravenous saline and gastric suction drainage, he was taken to the theatre and was operated on. The abdomen was opened in the middle line below the umbilicus and enormously distended coils of small intestine immediately protruded from the wound but, contrary to expectations, there was very little free fluid and no pus in the abdomen.

A hand was passed into the pelvis and the first thing noticed was that the bladder appeared to be full. On immediate enquiry being made he was said to have emptied the bladder before coming to the operating table. A loop of small intestine which was picked out of the pelvis showed a sealed and almost healed perforation, which had obviously been caused by the stick. Next a small piece of bark from a tree was found and removed. The rectum and sigmoid colon were now examined, but no sign of a perforation was found. Further exploration showed a loop of small intestine at first thought to be adherent to the back of the bladder, but when this was closely examined it was seen to pass into the bladder through a circular hole with a diameter of about 1½ inches. The edges of the hole in the bladder were thickened and gripped the bowel firmly. A definite lump could now be made out inside the bladder. An attempt was made to reduce the loop of small intestine out of the bladder, but this was not possible until the hole in the bladder had been enlarged by incision. After delivering the bowel from the bladder it was seen that a volvulus of this loop had occurred through a complete circle. The loop was black, thick and soggy and appeared to be completely dead, and it was thought that the only possible treatment would be resection and anastomosis.

While intestinal clamps were being prepared it was decided to deal with the bladder and in the meantime the affected loop was placed under warm moist towels. A Foley's catheter was inserted into the bladder and the rent in the bladder was closed with two layers of chromic catgut. As soon as this was completed the towels were removed from around the strangulated loop of intestine and, surprisingly in view of its previous appearance, it showed signs of recovering and of the circulation being restored.

While waiting to make sure that recovery would, in fact, take place and because there were now numerous vastly-distended coils of small intestine outside the abdomen which it would have been almost impossible to replace, it was decided to empty the small intestine of its contained fluid. At this stage the boy's condition was extremely bad. A small incision was made in the lowest loop of small intestine above the strangulation, a sucker was inserted, and a large quantity of foul fluid was sucked out. It was amazing to see the immediate change in the boy's condition, which improved so markedly that all need for undue haste fell away. As the suction proceeded 2 round-worms were felt at the end of the sucker and when the fluid had been removed these round-worms were also removed with the aid of forceps. The hole in the intestine was then closed, the strangulated loop was once more examined and found to be obviously recovering and now out of danger. The abdomen was closed in layers with catgut sutures. A drain was inserted down to the pelvis and was removed after 48 hours. The bladder was drained continuously for 7 days, and thereafter tidal drainage was carried out for 2 more days.

The boy began to run an irregular temperature on the 5th day after the operation and as no local cause was found in the abdomen or the pelvis it appeared probable that this rise of temperature might be caused by round-worms. Medical treatment was accordingly given for removing round-worms; this was successful in bringing

several away, after which his temperature immediately settled and his further progress was uninterrupted.

SUMMARY AND OBSERVATIONS

The case described showed several extraordinary features.

1. There is the long delay that occurred before urgent symptoms arose; it was only 24 hours before operation that danger signs appeared, namely 4 days after the injury.

2. There were 2 perforations of the bowel without general peritonitis occurring.

3. There was a large rupture of the bladder, which was apparently rapidly sealed by plugging of the hole by small intestine, thus preventing extravasation of urine into the peritoneal cavity. When the boy was questioned after the operation no history could be obtained of any difficulty in passing urine, even shortly after the accident.

4. An internal hernia into the bladder with the onset of acute symptoms precipitated by a volvulus must be extremely rare.

5. It is also of interest that a diagnosis was made of intestinal obstruction possibly due to round-worms.

BCG AND VOLE-BACILLUS VACCINES IN THE PREVENTION OF TUBERCULOSIS IN ADOLESCENTS

SUMMARY OF FIRST (PROGRESS) REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE*

In July 1949 the Medical Research Council, aware that a clinical trial of the BCG (Bacille Calmette-Guérin) and vole-bacillus vaccines was needed to provide essential information, appointed this committee to plan and direct an investigation. The following is the first report of this trial, which is still in progress, and presents preliminary findings at a time when every participant has been observed for 2½ years, and a few for 4 years. Since the trial is still in progress and the record cards are in continual use the statistics in this first report are based on representative samples of the record cards, except for the cases of tuberculosis amongst the participants, which have been completely enumerated and not estimated from samples.

The trial is designed to test the degree and duration of protection afforded by each of the two vaccines in adolescence, since the incidence and mortality in tuberculosis begin to rise at about the age of 15 from the low levels of childhood. Random vaccinated groups are to be compared with similar random unvaccinated groups and the participants are being followed up intensively for several years at least.

The Intake. The mass clinical test involved 56,700 boys and girls between 14 and 15½ years of age (mostly 14½-15) collected in 1950-1952 during their final year at 'secondary modern schools'. Of these, 23,400 were at schools at Birmingham, 18,800 at Manchester and 14,500 in the north of London—all large, densely-populated, industrialized areas.

Exclusions. The original intake of volunteers numbered 61,400, and the numbers were reduced by the following screening procedures:

1. Every child known to have tuberculosis in his immediate family or to have been in recent contact with a case at home was excluded.

2. A 35-mm. radiograph of the chest was taken of every child, and if any unusual appearance was noted the child was recalled for a full-plate chest radiograph. All children found or suspected to have any form of tuberculosis (apart from calcification of primary type) were excluded.

About 1,800 children were excluded on one or other of these grounds, 2,500 because they had not completed the initial radiographic examination and tuberculin tests, and 400 more for other reasons.

Classification by Tuberculin Test.

A Mantoux test (on the forearm) was then made of every entrant with 3·3 tuberculin units (3 TU), using 0·1 ml. of 1/3,000 OT; the greatest diameter of palpable infiltration at the end of 72 hours was recorded in mm. If there were no infiltration or if its diameter was less than 5 mm. the reaction to 3 TU was regarded as negative and another intracutaneous test was made on the same forearm with 100 TU, using 0·1 ml. of 1/100 OT; the greatest diameter of infiltration at the end of 72 hours was again recorded. Children with no infiltration, or with a diameter of infiltration less than 5 mm., at the second tuberculin test, were regarded as negative reactors to 100 TU.

The positive reactions numbered 22,600 (40%) 16,000 (28%) reacting to the weaker tuberculin (3 TU) and 6,600 (12%) to the stronger (100 TU) only.

The Vaccination. The negative reactors (60%) were divided into 3 strictly random* groups, which were respectively left unvaccinated (13,300), vaccinated with BCG (14,100), and vaccinated with vole bacillus (6,700). The dose of BCG (State Serum Institute, Copenhagen) was 0·1 ml. of vaccine (0·75 mg. of semi-dried weight bacilli per ml.) injected intracutaneously, and the vole-bacillus (Lister Institute, 2 mg. of wet weight bacilli per ml.) was introduced into the skin by a multiple-puncture instrument with 40 needles, projecting 2 mm. on release. The boys were vaccinated in the left deltoid region and the girls in the upper and outer part of the left thigh. The vaccination was carried out immediately after the result of the test with 100 TU had been read.

Second Examination. To observe the immediate effects of vaccination it was found possible in their last term at school to re-examine the children who entered the test in 1950 and 1951 (but, with a few exceptions, not the other participants). The examination included (*a*) a 35 mm. chest radiograph and, if indicated, a full-plate one, (*b*) tuberculin tests (as described above) except in those who had given strongly positive reactions at the first test, (*c*) the measurement of each BCG vaccination reaction, and the classification of each vole-bacillus reaction, and (d) the recording of local complications of vaccination.

Follow-up. Each participant was approached 3 times in the period of approximately 14 months after leaving school by the following channels:

(1) An enquiry form by post at approximately 4 months (repeated more than once if necessary. 77% returned at least one postal enquiry form within 18 months of their entry to the trial.)

(2) A visit from a local health visitor at approximately 10 months, making the same enquiries. (76% were thus visited at least once within 18 months of their entry to the trial.)

(3) At approximately 14 months (10-18 months) participants, now nearly all in employment, were invited to an examination by a mobile clinic including the same 4 items as the 'second examination' (see above) except that *every* participant was expected to undergo the Mantoux test(s). Those who did not attend were invited to do so

* From the full report in the *British Medical Journal* of 25 February 1956 (p. 413). Members of the Committee: Dr. P. D'Arcy Hart (chairman), Sir John Charles, Prof. R. Cruickshank, Dr. Marc Daniels (secretary until his death in 1953), Dr. W. Pointon Dick (resigned in 1951), Dr. J. E. Geddes, Prof. A. Bradford Hill, Sir Wilson Jameson, Dr. V. H. Springett, Dr. Ian Sutherland, Dr. A. Q. Wells, Dr. G. S. Wilson, Dr. T. M. Pollock (secretary).

* except that all the London children who were vaccinated, and for a short time all the Birmingham and Manchester vaccinees, received the BCG vaccine; and for a short time all the Birmingham and Manchester vaccinees received vole-bacillus vaccine.

when the team visited the district again later. (52% had a chest radiograph taken after leaving school, within 18 months of their entry to the test, and not less than 74% within 2 years of their entry.)

Within 18 months of their entry to the test 94% of the participants had been contacted either by return of a postal enquiry form, by interview with a health visitor, or by the taking of a chest radiograph.

The same cycle of enquiry and examination has been repeated in each subsequent 14-month period. Information has also been made available from local tuberculosis notification lists and local chest clinics. When participants have moved to other parts of the country (or, in a few cases, emigrated) postal enquiries have been sent them annually and arrangements made for annual X-ray examination and, if possible, tuberculin tests.

From these and other sources the records available for each case consisted of periodic radiographs, and the results of clinical examinations by one of the unit physicians or by other physicians, and of bacteriological or pathological examinations. Histological specimens were assessed by the National Institute of Medical Research. In cases of definite or suspected tuberculosis in BCG-vaccinated participants any cultures growing acid-fast bacilli were examined at Colindale for type, pathogenicity, etc. to exclude the possibility that the infecting organism was BCG itself. Similar cultures from vole-bacillus-vaccinated participants were examined at Oxford.

Grouping of Participants. For the purpose of the ensuing analyses, the participants were classified on entry to the trial into the following 5 groups, according to the result of tuberculin tests at the first examination and according as BCG vaccination or vole-bacillus vaccination or no vaccination was applied (see above):

1. Negative on entry (to 100 TU) and left unvaccinated	23%
2. Negative on entry (to 100 TU) and then given BCG vaccine	25%
3. Negative on entry (to 100 TU) and then given vole-bacillus vaccine	12%
4. Positive on entry to 3 TU and left unvaccinated	28%
5. Positive on entry to 100 TU (but negative to 3 TU) and left unvaccinated	12%
	100%

Deaths of Participants. The number of participants known to have died within 2½ years of entering the trial was 38. None of their deaths was due to any form of tuberculosis. The principal causes of death were accidents (13), malignant disease (7) and pneumonia (3). There appear to be no more than chance differences between the mortalities in the 5 groups.

Complications of Vaccination. A few cases of regional adenitis with cold abscess formation, following both BCG and vole-bacillus vaccination, were brought to the notice of the teams, but no evidence that this complication was common. At the second examination at school very few complications, with either vaccine, were seen; a few cases of delayed healing of the vaccination, with shallow ulceration, were noted; the regional glands were not examined as a routine measure. Certain other complications discovered later are described below.

CONVERSION TO TUBERCULIN-POSITIVITY FOLLOWING VACCINATION

Table I* gives the results of the tuberculin tests at the second examination at school (based on representative samples). The findings in the negative unvaccinated group illustrate the effect of natural infection with tubercle bacilli in the 3-5 months between the two examinations at school (coupled with variations inherent in the performance of the tuberculin test). At the second examination only 0·4% of these children were positive to 3 TU and a further 53% were positive to 100 TU only (Table I, Section A). In contrast, 85·8% of the BCG-vaccinated group were positive to 3 TU and a further 13·8% to 100 TU only, representing a total of 99·6%. From Section B of Table I it will be seen that 59·8% in the vole-bacillus-vaccinated group were positive to 3 TU and a further 34·6% to 100 TU only, giving a total of 94·4% converted. It was found that the earlier batches of vole-bacillus vaccine were below standard strength; when this vaccine was brought up to standard in September 1951 the percentages converted were almost identical with those for BCG vaccine.

Size of Reaction. The average diametres of BCG vaccination reactions at the second examination at school were 8·1 mm. for boys (on the arm) and 9·9 mm. for girls (on the thigh).

THE CASES OF TUBERCULOSIS

All the cases, definite and suspected, of tuberculosis were reviewed by an independent assessor who was unaware of the results of tuberculin tests and whether vaccination had been performed. It fell to the assessor also to distinguish between cases of tuberculosis present at the time of entry to the trial and those arising after entry, and to note the date when the disease first became manifest (e.g. when the first abnormal radiograph was taken). The latter date may be a considerable time after the true, but unknown, date of onset of the disease.

Cases of Tuberculosis present on Entry to the Trial

Besides the children excluded from the trial because they were found at the first examination at school to be suffering from definite or suspected tuberculosis, a further 85 cases discovered after the 56,700 participants had completed the first examination and entered the trial were adjudged by the independent assessor to have started before entry. These should not have been included in the trial at the first and were therefore excluded on discovery and are excluded from Tables I and II. (In 67 of the 85 cases the radiograph taken on entry showed on re-scrutiny appearances indicative of tuberculosis; in 14 more—13 of them non-pulmonary—symptoms were present before the participant entered the trial. The report states the reasons why the remaining 4 cases were adjudged by the assessor to have been present at the time of entry; these 4 children had—unknown to the assessor—all given a positive reaction to tuberculin on entry.)

* In the original report it is numbered as Table III.

TABLE I. PERCENTAGES OF PARTICIPANTS, IN THE NEGATIVE UNVACCINATED AND IN THE TWO VACCINATED GROUPS, WHO HAD POSITIVE TUBERCULIN REACTIONS AT THE SECOND EXAMINATION AT SCHOOL (ESTIMATES BASED ON REPRESENTATIVE SAMPLES OF PARTICIPANTS).

Section	*Skin-test and Vaccination Group (On Entry to the Trial)*	*At the Second Examination at School*			
		No. who Completed the Skin test	*Percentages with Positive Tuberculin Reactions*		
			Positive to 3 TU	*Positive Only to 100 TU*	*Total Positive*
A	Children admitted concurrently with those given BCG vaccine — Negative unvaccinated	5,700	0·4	5·3	5·7
	Negative, BCG vaccinated	7,300	85·8	13·8	99·6
B	Children admitted concurrently with those given vole bacillus vaccine — Negative unvaccinated	2,600	0·0	5·2	5·2
	Negative, BCG vaccinated	3,400	84·5	14·5	99·0
	Negative, vole-bacillus vaccinated	3,600	59·8	34·6	94·4
C	*Period of vaccination*				
	Jan., 1951-July 1951 — Vole-bacillus vaccinated	1,700	29·4	58·8	88·2
	Sept., 1951-Dec., 1952 — Vole-bacillus vaccinated	1,900	87·5	12·5	100·0

Tuberculous Lesions attributed to Vaccination

In 5 participants tuberculous lesions which developed after vaccination were regarded by the assessor as complications of vaccination, to be classed with the complications referred to above. They were two cases of erythema nodosum occurring 1 month after BCG vaccination, and 1 case of cervical and 2 of axillary tuberculous adenitis which occurred 3, 6 and 8 months after vole-bacillus vaccination. In addition 22 cases were discovered showing lesions indistinguishable from lupus vulgaris, severe enough to require treatment, at the site of the puncture vaccination with vole-bacillus vaccine. These 22 cases all occurred among the participants (4,100) given the vaccine after it had been brought up to standard (see above). No such cases were discovered in the children vaccinated with BCG vaccine. All these 27 cases are excluded from Tables I and II. It is emphasized that there was no evidence that any of the other cases of tuberculosis in vaccinated participants were due to the vaccinating organism.

Incidence of Tuberculosis in the first 2½ years

By the end of June 1955 every participant had been in the trial for 2½ years, and the great majority of cases of tuberculosis starting within 2½ years of entry may be presumed to have come by now (January 1956) to the notice of the teams.

A total of 165 cases of definite tuberculosis started within the 30 months of entry to the trial (75 discovered by the teams radiologically and 90 discovered by the National Health Service), and a further 9 were assessed as possible tuberculosis. There were no deaths from tuberculosis. The number of cases in the 5 skin-test and vaccination groups are given in Table II*. Section A shows an annual incidence of 1·94 per 1,000 in the tuberculin-negative unvaccinated group, compared with 0·37 in the BCG-vaccinated group. (The possibility of this having occurred by chance is less than 1 in a million.) The annual incidence in the group initially positive to 3 TU was 1·75 per 1,000, compared with 0·74 in the group positive to 100 TU. The difference in incidence between the two positive groups, and also between the negative unvaccinated group and those positive only to 100 TU, is statistically significant (0·01>P>p·001). The incidence in the BCG-vaccinated group is also substantially and significantly lower than that in the group initially positive to 3 TU (0·001<P), but, while rather less, does not differ substantially from that in the group positive only to 100 TU (0·2>P>0·1).

Section B of Table II shows an annual incidence of 2·06 per 1,000 in the negative unvaccinated group, compared with 0·44 in the vole-bacillus-vaccinated group. (The possibility of this difference having occurred by chance is less than 1 in 10,000.) The difference between the annual rates for the vole-bacillus-vaccinated group (0·44) and for the concurrent group of BCG-vaccinated children (0·31) does not attain statistical significance.

If the 9 cases in which the assessor was in doubt over the diagnosis were included with the definite cases, the above comparisons would remain practically unaltered.

Of the 20 definite cases of tuberculosis in the vaccinated groups there was evidence in all except one (in a vole-bacillus-vaccinated participant, in whom no tuberculin test was made before the disease developed and no vaccination reaction was seen at the first re-examination, which was 2 years after vaccination) that the individuals had been satisfactorily vaccinated, as judged by the usual criteria. In one of the 20 (a BCG-vaccinated participant)—the only one known to have developed within 6 months of vaccination—it was considered that the disease might well have arisen before any protection had been conferred.

The Forms of Tuberculosis. In 104 of the 165 cases (63%) the form of tuberculosis that developed (or the major form) was pulmonary tuberculosis. There is no evidence of important differences between the 5 groups in the ratio of pulmonary to total cases (though the numbers of cases in the 2 vaccinated groups are small). Tuberculous meningitis (3) and miliary pulmonary tuberculosis (3) occurred in 6 of the 64 cases in the negative unvaccinated group. None occurred in any of the other groups.

Severity of Pulmonary Lesions. No important difference between the 5 groups was found in respect of extent of lesion or cavitation. Nor did a consideration of the treatment ordered by the physician responsible for the care of the patient reveal any important differences between the groups in regard to the severity of the lesions.

Other Particulars. Particulars are given in the report concerning the bacteriological and pathological investigations that were carried out, particulars bearing on the reliability of the independent assessments, and particulars concerning the starting point of the illness relative to the date of entry to the trial.

Supplementary Information on Cases of Tuberculosis starting after the first 2½ years. Some preliminary information is available on the continuance, beyond the first 2½ years, of the protection afforded by the vaccines. All the participants have now (January 1956) been in the trial for 3 years, some 4 years, and a few have completed 5 years. All cases of tuberculosis are being assessed as they come to the notice of the teams. Of the 75 cases that are known (up to date) to have started between 2½ and 4 years after entry, 38 are in the negative unvaccinated group, 5 in the negative BCG-vaccinated group, 0 in negative vole-bacillus vaccinated group, 24 in the positive to 3TU group and 8 in the positive only to 100 TU group. These figures afford no evidence of any diminution in the efficacy of either of the two types of vaccine up to 4 years.

TABLE II. CASES OF TUBERCULOSIS STARTING WITHIN TWO AND A HALF YEARS OF ENTRY TO THE TRIAL

Section	Skin-test and Vaccination Group	Estimated No. of Participants	Definite Cases of Tuberculosis: No. Starting within 30 Months	Definite Cases of Tuberculosis: Annual Incidence per 1,000 Participants	Possible Cases of Tuberculosis Starting within 30 Months
A	Children admitted concurrently with those given BCG vaccine: Negative unvaccinated	13,200	64	1·94	2
	Negative, BCG vaccinated	14,100	13	0·37	2
	Positive to 3 TU	15,800	69	1·75	3
	Positive only to 100 TU	6,500	12	0·74	1
B	Children admitted concurrently with those given vole-bacillus vaccine: Negative unvaccinated	6,400	33	2·06	2
	Negative, BCG vaccinated	6,400	5	0·31	1
	Negative, vole-bacillus vaccinated	6,400	7	0·44	1
	Positive to 3 TU	8,600	37	1·72	2
	Positive only to 100 TU	3,500	6	0·69	0
C	All participants included in the above comparisons†	56,000	165	—	9

† That is, all participants in Section A plus the vole-bacillus-vaccinated group in Section B.

DISCUSSION

The early results of the present trial provide clear evidence, for a period of 2½ years, of the efficacy of BCG vaccination, and also of

* Table IV in the original report.

vole-bacillus vaccination, in the prevention of tuberculosis in a group of adolescents living the ordinary urban and suburban life in an English industrial community with well-developed health services and with relatively low tuberculosis incidence and mortality.

The trial was confined to a narrow and susceptible age-group, viz. children nearly all between 14½ and 15 years, in the final year at 'secondary modern schools' at North London, Birmingham and Manchester, who volunteered with parental consent. The 56,700 participants came from a wide range of social and economic backgrounds and were initially free from active tuberculosis and from known contact with the disease at home.

All the participants are being kept under observation and when the trial was planned emphasis was laid on the need to detect and study cases of tuberculosis rather than deaths; in the event 165 participants are known to have developed tuberculosis within 2½ years of entering the trial, but there was no death from the disease during this period. A much longer period of observation will be necessary, but the early results are of sufficient importance to be considered and recorded. The scope of the report is also limited because the numbers of participants (though not the number of cases of tuberculosis) had to be estimated from representative samples of the records.

It is probable that few cases of tuberculosis have escaped detection, and there has been close correspondence between the diagnoses of the independent assessor, unaware of the vaccination history of the children, and those of the chest clinic and other physicians responsible for the investigation and treatment of the cases.

Protection afforded by Vaccination

In the first 2½ years the cases of tuberculosis that occurred in the tuberculin-negative unvaccinated group amounted to 1·94 per 1,000 per annum, as compared with a rate of 0·37 per 1,000 in the tuberculin-negative who received BCG vaccine (approximately one-fifth). Similarly the group of tuberculin-negative who received vole-bacillus vaccine gave an annual incidence of 0·44 per 1,000, or approximately one-fifth of the incidence of 2·06 per 1,000 amongst those admitted concurrently in the tuberculin-negative group. Thus the protective value of both vaccines was shown to be substantial. Both vaccines appeared to confer protection within 6 months, the protection was still substantial at 2½ years, and supplementary incomplete information suggests that the protection is maintained up to 4 years. (Aronson and Aronson—*J. Amer. Med. Assoc.* 1952, **58,** 255—reported that in North American Indians a substantial degree of protection from BCG vaccination was maintained for at least 10 years. The present report records the results of a few other trials of BCG vaccination in general population groups in other countries, in which tuberculin-negative subjects were selected by a random process either for vaccination or to be left unvaccinated).

The forms of tuberculosis and their severity were studied and have appeared to be similar in the vaccinated groups and the negative unvaccinated group. However the 3 cases of tuberculous meningitis and the 3 of miliary pulmonary tuberculosis were confined to the negative unvaccinated group.

Complications of Vaccination

With both vaccines occasional cases of regional adenitis and delayed healing of the vaccination lesion were recorded. In addition 2 cases of erythema nodosum developed after 4 weeks in the 14,100 participants given BCG vaccine. These complications have to be set against the efficacy of the vaccines in preventing tuberculosis. With the vole-bacillus vaccine the findings of earlier workers have been confirmed—that lesions indistinguishable from lupus vulgaris occasionally develop at the site of vaccination. These lesions have been severe enough to require treatment in 22 of the 6,400 participants given the vole-bacillus vaccine. This vaccine was given by multiple puncture and it is possible that the intracutaenous method will not produce this complication.

Incidence of Tuberculosis in those initially Tuberculin Positive

Considerable attention was given in this investigation to the behaviour in this report of the 22,300 participants who were tuberculin-positive on entry. Among those with a positive reaction to 3 TU on entry the annual incidence of tuberculosis (2½ years) was 1·75 per 1,000, as compared with 0·74 in those who on entry were negative to 3 TU but positive to 100 TU. Thus, as a group, those positive to 100 TU only were less likely to contract tuberculosis than those positive to 3 TU. Moreover the incidence of tuberculosis within the group positive to 3 TU was associated with the intensity of the initial reaction to tuberculin. For those with induration of 5-14 mm. to 3 TU the annual incidence was 0·78 per 1,000 (almost the same as for those initially positive only to 100 TU), but for those with larger reactions to TU the incidence was 2·93 per 1,000 (which is higher even than in the negative unvaccinated group).

These findings call for more investigation; it is hoped that further information from the present trial may become available in a later report.

Assessment of the Benefits of Vaccination

According to the present results, if *none* of the tuberculin-negative entrants had been vaccinated, 165 cases of tuberculosis would have been expected among them within 2½ years of entry; if *all* of them had received BCG vaccine, 30 cases would have been expected—a reduction of 82% in the expected incidence of *tuberculosis in the tuberculin-negative group.*

However, many of the children entering the trial were tuberculin-positive and thus not eligible for vaccination. They produced 81 cases of tuberculosis in 2½ years; including these the expected reduction in the total number of cases in 2½ years if all the tuberculin-negative entrants had been vaccinated would have been from 246 (165+81) to 111 (30+81)—a reduction of 55% in the incidence of tuberculosis in the tuberculin-negative and tuberculin-positive groups combined.

This estimate, however, has been calculated after the exclusion of 134 previously unsuspected cases of definite tuberculosis which were present on entry to the trial (nearly all detected from the initial radio-graphic examination at school). If the preliminary X-ray had not been taken many of the 134 cases would apparently have arisen *after* entry and would have increased the total cases amongst those initially tuberculin-positive from 81 to a figure of the order of 200. The apparent reduction in the total number of cases within the 2½ years, as a result of giving BCG to all those initially tuberculin negative, would, in the absence of an initial radiograph, have been of the order of 35% (from 165+200 to 30+200). As a corollary, in any scheme of vaccination in adolescence, X-ray examination and follow-up of those found at the outset to be tuberculin-positive, particularly those with strong reaction, should be considered.

The benefit to be expected from BCG vaccination may also be experienced in terms of the administrative action required. The expected reduction of 135 cases in the first 2½ years would have resulted from the tuberculin-testing of 56,000 school-children and the BCG vaccination of the 33,700 negative reactors. This corresponds to the prevention of 1·6 cases annually (for 2½ years) among every 1,000 children given BCG vaccine, or the prevention of 1·0 cases of tuberculosis annually (for 2½ years) for every 1,000 children given tuberculin tests preparatory to vaccination. The expected results if vole-bacillus vaccine were used in place of BCG would be very similar.

It is to be borne in mind that the participants were vaccinated towards the end of their 15th year, by which time 40% were tuberculin-positive. The experience of this trial indicates that it might be desirable to vaccinate school-children at an early age, before so large a proportion of them had been infected naturally. However, not until further information becomes available on the duration of the protection afforded by vaccination, and this is considered in relation to the proportion of children who are tuberculin-positive at different ages, will it be possible to judge the optimum age at which to institute a scheme for a single vaccination of adolescents.

Finally it should be borne in mind that the cases discovered in the group tuberculin-negative on entry and remaining unvaccinated are manifestations of tuberculosis appearing within a few years of natural first infection, and that the protection shown to have been afforded by vaccines concerns these manifestations. The investigation provides no information about the development of tuberculosis in the vaccinated participants during later life.

The trial is still in progress, and later reports will contain detailed analyses over longer periods of time.

REVIEWS OF BOOKS : BOEKRESENSIES

THE MENTALLY RETARDED CHILD, FOR PARENTS

The Mentally Retarded Child. A Guide for Parents. By Abraham Levinson, M.D. Pp. 128. 12s. 6d. London: George Allen & Unwin Ltd. 1955.

Contents: 1. The Parents of the Mentally Retarded Child. 2. Advice to Parents. 3. Historical Survey. 4. What is Mental Retardation? 5. The Brain. 6. How the Doctor Makes a Diagnosis. 7. Team Work. 8. Early Recognition. 9. Causes of Mental Retardation. 10. Prevention of Mental Retardation. 11. Treatment of Mental Retardation. 12. Education of the Mentally Retarded Child. 13. Vocational Training and Guidance. 14. Outlook for the Future. 15. Community and State Responsibility. 16 Research. 17. The Dr. Julian D. Levinson Research Foundation. Organizations. Index.

This is a valuable book, written primarily for parents, though with a fair resumé of the anatomy, physiology and pathology of the causes of mental retardation.

Written by an American, it has been annotated by a psychiatric social worker in England in order to clarify the differences between the social and educational arrangements in the two countries. It is in the educational sphere, both of parent and child, that the main problem exists.

Much remains to be done in South Africa on this problem, and this book can be strongly recommended to all parents of retarded children. Upon the parents falls the main burden, and they should be encouraged to form groups for the discussion of their difficulties, and to bring pressure to bear to improve facilities for the handling of these handicapped children.

P.V.S.

Lipponcott's Quick Reference Book for Nurses. By Mary E. Allanach, A.M., R.N.; Elizabeth S. Gill, B.S., R.N.,; Helen F. Pettit, A.M., R.N.; Dorothy E. Reilly, M.S., R.N. and Nelda Ross Larsson, M.S. Seventh Edition. Pp. 727. 32s. net. London: Pitman Medical Publishing Co. Ltd.

Contents: Section 1. Pharmacology. Section 2. Medical and Surgical. Section 3. Nursing Technics. Section 4. Diet Therapy. Section 5. Maternity Nursing, Including Child Care. Appendix. Index.

This book has proved its usefulness to thousands of nurses since it first appeared in 1933. Then the authors made no claim to originality of material but sought to provide a book which would live up to its name of 'quick reference'.

With the changing times, the introduction of new nursing techniques and the general progress of medicine, this new edition has brought the whole volume up to date. Although the revision has entailed considerable work and the complete resetting of the type, it has also made possible such rearrangement as was necessary to improve a book which had already proved its worth.

There is little need to go into detail regarding the scope of the book—a glance at the chapter titles above is sufficient to indicate this. It is very complete and is a first class book of 'quick reference'. As such it will continue to help the present generation of nurses.

A.H.T.

CORRESPONDENCE : BRIEWERUBRIEK

THE 'MUNCHAUSEN SYNDROME'

To the Editor: Judging from letters appearing in recent correspondence columns of the *British Medical Journal* and the *Lancet*, considerable interest has been aroused in patients with the so-called Munchausen syndrome who contrive to have themselves admitted successively to several hospitals. They are reinvestigated on each occasion at the expense of the Health Service, and obtain free board and lodging for lengthy periods in exchange for the discomfort of a few needle pricks.

Recently a European male of about 25 years was admitted to this hospital after an alleged convulsion with loss of consciousness. He gave a Kimberley address and said he was a miner. Examination revealed no neurological abnormality and the patient denied a previous ictus. He had evidence of heart disease (mitral and aortic stenosis and aortic incompetence) of which he said he was quite unaware. Lumbar puncture was normal. While in the ward he developed a transient hemi-anaesthesia.

On the day of discharge from Groote Schuur Hospital, he was admitted to the Conradie Hospital with precisely the same story, having been found unconscious near the gate. We now have reason to believe him to be an in-patient in the Provincial Hospital in Port Elizabeth, having been discovered yet again unconscious in a street.

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7 April 1956

SICKLE-CELL ANAEMIA IN A YOUNG COLOURED MALE

To the Editor: It was with more than the usual interest that I read the paper of Dr. Segal and collaborators[1] on the fourth case of sickle-cell anaemia, reported from South-Africa. In different parts of the Belgian Congo we have observed several hundreds of cases of real homozygous sickle-cell anaemia and in the light of this experience we feel that the case of Dr. Segal presents some aberrant features that make the diagnosis of homozygous sickle-cell disease very unlikely.

In the first instance there is the age of the patient: less than 1% of our patients reach the age of 20 and still less have living children. Secondly: a haemoglobin level of 10·5 g % is excessively rare in our experience and 14 g (without transfusion) has definitely never been noted. There is finally the rather high figure for alkali-resistant haemoglobin (23%) which is unusual, although not impossible, in sickle-cell anaemia.

The almost perfect state of health of the patient is another puzzling feature and the enlarged spleen is a rare symptom in affected adults. The results of the blood studies on the members of the family are not clearly quoted. Of the patient's three children one was found to have sickle-cells. Were the other two negative or were they simply not available for study? If the former alternative is true, then it can no longer be accepted that the father is homozygous for the sickle-cell gene.

The occurrence of a series of so highly exceptional characteristics in one of the four South African cases is probably not mere coincidence and this should stimulate the authors to re-examine their patient and his family. A diagnosis of sickle-cell thalassaemia disease seems to show more consistency with the clinical picture and the haematological data. The statement of the authors that all the haemoglobin present was sickle haemoglobin, is clearly an exaggeration, as two paragraphs further down they cite that 23% was of the alkali-resistant type.

The real percentage for S haemoglobin is thus 76% (or even less if a small fraction of Hb A is also present). This percentage is within the range found in sickle-cell thalassaemia disease. The latter is not always easily distinguishable from homozygous sickle-cell disease by routine paper electrophoresis. Family studies may be essential in some borderline cases.

Edington and Lehmann[2] have also described asymptomatic cases of sickle-cell disease, but in subsequent communication[3] they reported that family studies had brought to light a thalassaemia-like gene. Singer[4] and associates also supply descriptions of clinically almost asymptomatic cases of sickle-cell thalassaemia disease.

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26 March 1956

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2. Edington, G. M. and Lehmann, H. (1955): Brit. Med. J. **1**, 1308.
3. *Idem*, (1955): *Ibid.*, **2**, 1328.
4. Singer, K., Singer, L., and Goldberg, S. R. (1955): Blood, **10**, 405.